

Evaluation of the Relationship Between Platelet Indices and Mitral Restenosis After Percutaneous Mitral Balloon Valvuloplasty

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Abstract

Objectives: Percutaneous mitral balloon valvuloplasty (PMBV) has been established as an effective and safe treatment modality for symptomatic patients with severe rheumatic mitral stenosis. Wilkin scores ≤ 8 are associated with higher rates of procedural success and lower rates of restenosis. It is well-known that platelets have a substantial role in thromboembolic complications of rheumatic mitral stenosis and various studies have showed that increases platelet (PLT) activity in rheumatic mitral stenosis. The aim of this study was to assess the usefulness of PLT indices as a predictor of restenosis in patients who underwent PMBV.

Materials and Methods: We retrospectively enrolled 178 consecutive patients who underwent PMBV. Patients were classified into two groups. The study group (n=21) included patients whom we performed redo PMBV during their follow-ups as a result of mitral restenosis following previous PMBV (index procedure) and the control group (n=157) included patients who did not undergo a redo PMBV. PLT indices including PLT count, Plateletcrit (PCT) and mean platelet volume (MPV) values were evaluated in these groups.

Results: In the study group, PLT count (210±49 vs 241±62, p=0.010), PCT [0.203 (0.173-0.230) vs 0.260 (0.243-0.290), p<0.001] and MPV [9.7 (8.7-11.1) vs 10.5 (9.8-12.0), p=0.021] values were significantly higher in the restenosis group when compared to the control group. Receiver operating characteristic analysis showed cut-off values for MPV crossed



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Abstract

the curve at 9.65 (sensitivity 81.0% and specificity 49.7%) and for PCT crossed the curve at 0.241 (sensitivity 76.2% and specificity 87.9%).

Conclusion: PLT indices including PLT count, MPV and PCT might be feasible and easy parameters to predict possible restenosis after PMBV.

Keywords: Rheumatic mitral stenosis, platelet, plateletcrit, percutaneous mitral balloon valvuloplasty

Introduction

Percutaneous mitral balloon valvuloplasty (PMBV) is an effective and safe treatment modality for symptomatic patients with severe rheumatic mitral stenosis in clinical practice⁽¹⁻³⁾. Studies in literature demonstrated that pre-procedural clinical and echocardiographic characteristics and post-procedural outcomes had strong association in between⁽⁴⁾. In current clinical practice, Wilkins score (WS) is used to determine the morphology of mitral valve in transthoracic echocardiography (TTE) and score includes leaflet thickening, calcification, mobility and subvalvular fusion^(5,6). $WS \leq 8$ is associated with higher rate of procedural success and lower rate of restenosis⁽⁷⁾. Long-term adverse events after PMBV including mitral restenosis, occurrence of mitral regurgitation (MR), or progression of other valvular diseases were evaluated in previous studies. According to those studies, the incidence of restenosis was approximately 40% depending on the patient population, valve morphology, and duration of follow-up. In addition, major predictive factors with regard to being free from restenosis were $WS \leq 8$ and post-procedural mitral valve area (MVA) $\geq 2.0 \text{ cm}^2$ ^(8,9).

Platelets have substantial role in thromboembolic complications of rheumatic mitral stenosis. Evidence by *in vivo* hemostatic markers revealed that rheumatic mitral stenosis was associated with increased platelet (PLT) activity^(10,11). Increased PLT activity caused increased production of thromboxane A2 and beta thromboglobulin, which resulted in a pro-thrombotic state in this patient population⁽¹²⁾. PLT indices such as PLT count, mean platelet

volume (MPV), and plateletcrit (PCT) are measured by automated blood cell analyzers and are reliable markers of PLT activity.

Therefore, in this study, we aimed to evaluate the usefulness of PLT indices as a predictor of restenosis and assessed long-term outcomes in patients who underwent PMBV.

Materials and Methods

Study Population

We retrospectively enrolled 178 consecutive patients presenting with symptomatic rheumatic mitral stenosis with favorable valve morphology, who underwent PMBV at our hospital between January 2010 and December 2019. Informed consent was obtained from all patients in accordance with a protocol approved by the local ethics committee (Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee, decision no: 2020/58, date: 18.08.2020). Patients with MR more than mild or evidence of left atrial (LA) thrombus by transesophageal echocardiography (TEE) were excluded from the study because those parameters were contraindications for PMBV. Patients with concomitant valve disease requiring surgical intervention and patients indicated for coronary artery bypass surgery were also excluded.

Then, patients were classified into two groups based on their follow-up findings. The study group was defined as patients whom we performed redo PMBV during their follow-up as a result of mitral restenosis

following previous PMBV (index procedure) and the control group was defined as patients who did not undergo a redo PMBV. In the study group, restenosis was defined as a decrease in MVA $>50\%$ after the index PMBV together with MVA ≤ 1.5 cm² during follow-up. For each group, demographic characteristics, past medical records, laboratory values, procedural information, TTE and TEE parameters were noted. Echocardiographic evaluation included left ventricular ejection fraction (LVEF), MVA, systolic pulmonary artery pressure (sPAP), mean diastolic mitral gradient, WS, and LA diameter.

Laboratory Measurements

Blood samples were drawn from the ante-cubital vein after a 12-hour fasting period and at most 24 hours before the procedure. PLT indices were measured in a blood sample collected in dipotassium EDTA tubes. An automatic blood counter (Sysmex, XT-2000i) was used for whole blood counts. PLT indices were measured within 30 minutes after sampling to prevent EDTA-induced PLT swelling. PCT, which defines the mass of PLT, is the volume occupied by PLT in the blood as a percentage. PCT was estimated according to the formula of $PCT = PLT \text{ count} \times MPV / 10.000$ ^(13,14).

Echocardiographic Assessment

All patients underwent TTE examination using a GE Vingmed Vivid 5 echocardiography device (GE Vingmed Ultrasound, Horten, Norway) before the procedure. MVA and other conventional echocardiographic measurements in our center are routinely performed according to American Echocardiography Society criteria in daily practice⁽¹⁵⁾. Mitral valve apparatus morphology was evaluated by using WS which included semi-quantitative assessment of leaflet mobility and thickening, subvalvular changes, and valve calcification according to previous definitions⁽⁶⁾. In addition, all patients routinely undergo TEE examination in our center within 24 hours before the planned procedure in order to rule out left atrial or appendage thrombosis and assessment of mitral annular diameter and morphology

of atrial septum. Pre-procedural echocardiographic parameters were noted for every patient.

Procedural Technique

PMBV was performed via the trans venous (antegrade) approach through the femoral vein using a transeptal Brockenbrough needle as previously described⁽¹⁶⁾. Initial balloon size was selected according to body surface area. Maximum balloon size was determined by the following formula: $[\text{patient height (cm)} / 10 + 10]$ ⁽¹⁷⁾. All procedures were performed under TEE guidance. Procedure related mitral valve regurgitation was assessed by using echocardiography. According to our study, successful PMBV was defined as post-procedural MVA ≥ 1.5 cm² by Gorlin formula and post-procedural MR less than moderate by echocardiographic or angiographic evaluation immediately after PMBV.

Statistical Analysis

Statistical analysis was made using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, New York, USA). Data were expressed as “n (%)” for categorical variables. The Pearson chi-square and Fisher exact tests were performed for categorical variables. After fitness to normal distribution was analyzed with the Kolmogorov-Smirnov test, data were expressed as “median (25th and 75th percentiles)” for variables without a normal distribution and mean \pm standard deviation for variables with normal distribution. While the Student-t test was used to compare quantitative variables with normal distribution, the Mann-Whitney U test was used to compare quantitative variables without a normal distribution. Receiver operating characteristic (ROC) analysis was conducted to determine the optimal PCT and MPV value to indicate mortality in terms of both sensitivity and specificity. The long-term restenosis curve for both MPV and PCT was analyzed using the Kaplan-Meier method, and statistical assessment was performed using the log-rank test. A p value <0.05 was considered to be statistically significant.

Results

Baseline clinical and demographic characteristics of each group were provided in Table 1. There were no significant differences between two groups in terms of baseline clinical and demographic characteristics. On the other hand, the incidence of diabetes mellitus (DM) [7 (4.5%) vs 4 (19.0%), $p=0.028$] and the presence of atrial fibrillation (AF) [28 (17.8%) vs 12 (57.1%), $p<0.001$] were significantly higher in the study group compared to the control group. One hundred and fifty-seven patients without restenosis had PMBV between 27 and 84 months ago and restenosis was not detected during their follow up. Twenty-one patients with restenosis had previous PMBV between 36 and 60 months ago and had their redo PMBV in our hospital during their follow-up.

Table 1. Baseline demographic and clinical variables of study population

	Restenosis (-) (n=157)	Restenosis (+) (n=21)	p value
Age (years)	42±11	41±11	0.536
Sex - female, n (%)	127 (80.9)	19 (90.5)	0.227
NYHA classification before PMBV			
NYHA I	10 (6.4)	2 (1.4)	0.335
NYHA II	101 (64.3)	11 (9.8)	
NYHA III	42 (87.5)	6 (12.5)	
NYHA IV	4 (2.5)	2 (9.5)	
Coronary artery disease (n, %)	6 (3.8)	1 (4.8)	0.591
Prior cerebrovascular event (n, %)	6 (3.8)	0 (0)	0.465
Diabetes mellitus (n, %)	7 (4.5)	4 (19.0)	0.028
Hypertension (n, %)	16 (10.2)	5 (23.8)	0.080
Peripheral embolic event (n, %)	1 (0.6)	1 (4.8)	0.223
Presence of atrial fibrillation (n, %)	28 (17.8)	12 (57.1)	<0.001
Follow-up period (months)	60 (27 - 84)	48 (36-60)	0.377

NYHA: New York Heart Association, PMBV: Percutaneous mitral balloon valvuloplasty, n: Number
Important p values are written in bold.

In the study group, PLT (210±49 vs 241±62, $p=0.010$), PCT [0.203 (0.173-0.230) vs 0.260 (0.243-0.290), $p<0.001$] and MPV [9.7 (8.7-11.1) vs 10.5 (9.8-12.0), $p=0.021$] values were significantly higher when compared to the control group. Baseline laboratory values of both groups were shown in Table 2.

Although baseline MVA and echocardiographic parameters were similar in both groups, WS was significantly higher in the study group compared to the control group [8 (7-9) vs 9.5 (8-10), $p=0.042$]. Baseline TTE and TEE measurements were shown in Table 3.

Procedural and post-procedural data for the patients were shown in Table 4. The control group patients without restenosis included data for their PMBV. The study group patients who had restenosis included data for their redo PMBV. The successful PMBV was achieved in 17 (81.0 %) patients of the study group and 138 (87.9 %) patients of the control group. Comparison of outcomes of procedures and post-procedural TTE measurements were shown in Table 4. Procedural

Table 2. Laboratory parameters of patients with and without restenosis

	Restenosis (-) (n=157)	Restenosis (+) (n=21)	p value
Creatinine (mg/dL)	0.7 (0.6-0.81)	0.7 (0.61-0.76)	0.340
Total cholesterol (mg/dL)	177 (163-195)	149(119-167)	0.067
LDL (mg/dL)	105 (91-124)	77 (58-93)	0.057
HDL (mg/dL)	49±14	54±17	0.610
Triglyceride (mg/dL)	114 (71-145)	84 (44-101)	0.201
Leukocyte (10 ³ /mL)	7.32 (6.37-9.26)	7.75 (6.84-8.26)	0.558
Platelet (10 ³ /mL)	210±49	241±62	0.010
Plateletcrit (%)	0.203 (0.173-0.230)	0.260 (0.243-0.290)	<0.001
Mean Platelet Volume (fL)	9.7 (8.7-11.1)	10.5 (9.8-12.0)	0.021
Hemoglobin (g/dL)	12.73±1.84	12.44±1.54	0.495

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, n: Number
Important p values are written in bold.

success rate and post-procedural TTE parameters except the mean gradient were similar between both groups. On the other hand, decrease in trans-mitral gradient was found to be significantly lower in the study group compared to the control group [5 (4-6) vs 6 (5-7), $p=0.004$].

ROC analysis was conducted to determine the optimal MPV and PCT cut-off values to indicate restenosis. The highest combined sensitivity and specificity values for MPV crossed the curve at 9.65 (sensitivity 81.0% and specificity 49.7%) (Table 5). The area under the curve (AUC) was 0.656 (95% CI: 0.541-0.770, $p=0.021$). The highest combined sensitivity and specificity values for PCT crossed the curve at 0.241 (sensitivity 76.2% and specificity 87.9%). The AUC was 0.826 (95% CI: 0.700-0.952, $p<0.001$) (Figure 1).

A Kaplan-Meier survival analysis also revealed that long term restenosis rate was found to be significantly

Table 3. Pre-procedural transthoracic and transesophageal echocardiographic parameters of study groups prior to their first percutaneous mitral balloon valvuloplasty

	Restenosis (-) (n=157)	Restenosis (+) (n=21)	p value
Ejection fraction (%)	60 (60-65)	65 (60-65)	0.296
TTE			
sPAP (mmHg)	42 (35-55)	45 (39-55)	0.453
LA diameter (cm)	4.5 (4.2-4.8)	4.7 (4.4-4.9)	0.111
Wilkins score	8 (7-9)	9.5 (8-10)	0.042
Planimetric MVA (cm ²)	1.1 (1.0-1.2)	1.1 (1.0-1.3)	0.417
MVA PHT (cm ²)	1.1 (0.9-1.3)	1.1 (1.0-1.2)	0.739
Mean gradient (mmHg)	11 (9-14)	11 (10-13)	0.532
TEE			
sPAP (mmHg)	50 (40-60)	47 (35-55)	0.589
Mean gradient (mmHg)	13 (11-18)	15.5 (11-20)	0.390
Planimetric MVA (cm ²)	1.0 (0.9-1.2)	1.0 (0.85-1.2)	0.528
MVA PHT (cm ²)	1.1 (0.98-1.2)	1.0 (0.9-1.3)	0.715
Wilkins score	8 (7-8.5)	8 (7.5-9)	0.144

TTE: Transthoracic echocardiography, sPAP: Systolic pulmonary artery pressure, LA: Left atrium, MVA: Mitral valve area, PHT: Pressure halftime

higher in patients with higher PCT (Log-Rang $p<0.001$) and MPV (Log-Rang $p<0.001$) values (Figure 2 A, B).

Discussion

This study analyzed the predictors of mitral restenosis in patients who underwent PMBV. It demonstrated that PMBV was performed in eligible patients with procedural success rate of 87.0%. According to our study, 21 out of 178 patients developed mitral restenosis following successful PMBV. Additional to that, patients who had restenosis after PMBV had significantly higher value in PLT indices such as PLT, PCT and MPV.

PMBV has been a choice for the treatment of patients with symptomatic significant mitral stenosis with favorable mitral valve morphology. Despite its favorable outcomes, studies have revealed high rates of restenosis with adverse clinical events in patients who underwent successful PMBV⁽¹⁸⁻²¹⁾. According to a study conducted by Farhat et al.⁽²²⁾, incidence of restenosis after PMBV has been reported between 3% and 70% in one to three years. They also demonstrated that the risk of restenosis

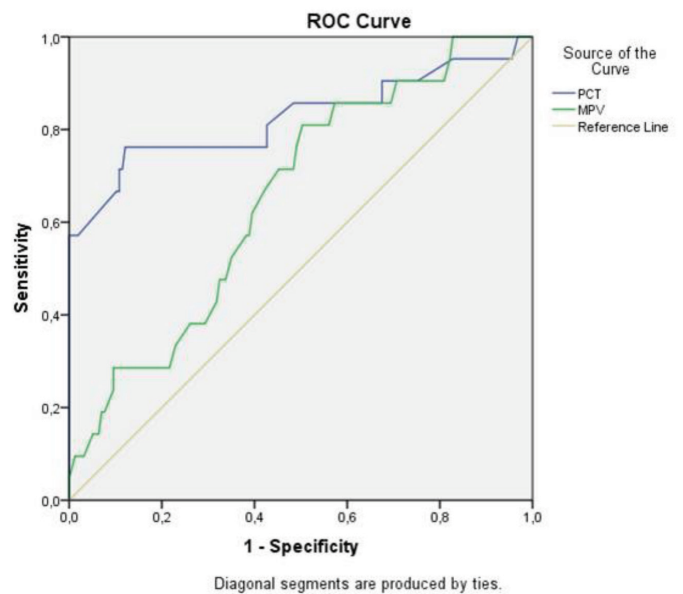


Figure 1. ROC analysis was conducted to determine the optimal MPV and PCT cut-off values to indicate restenosis
ROC: Receiver operating characteristic, MPV: Mean platelet volume, PCT: Plateletcrit

increased progressively during follow-up of these patients (77% at 10 years, 46% at 15 years and 18% at 18 years, respectively). In another study by Hernández et al.⁽²⁾, older patients (mean age 53 years) had higher rate of restenosis

(39% restenosis rate at 7 years). Outcome of those studies demonstrated that major predictor factor for restenosis as WS, especially pre-procedural WS ≥ 8 was associated with higher risk of restenosis. Previous studies also reported that post-procedurally estimated MVA and restenosis were

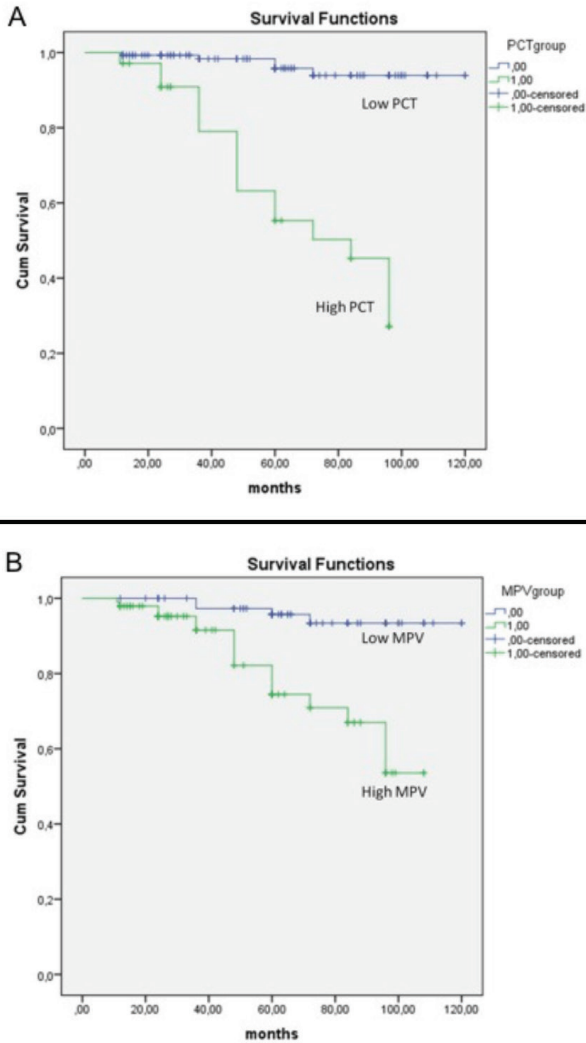


Figure 2. A Kaplan-Meier survival analysis also revealed that long term restenosis rate was found to be significantly higher in patients with higher PCT (A) and MPV (B) values
PCT: Platelecrit, Cum: Cummulative, MPV: Mean platelet volume

Table 4. Procedural and post-procedural data for the groups. Restenosis (+) group includes data of redo PMBV and restenosis (-) group includes data of PMBV

	Restenosis (-) (n=157)	Restenosis (+) (n=21)	p value
Post-procedural TTE			
Ejection fraction (%)	60 (60-65)	60 (60-65)	0.967
sPAP (mmHg)	30 (25-38)	35 (29-40)	0.281
LA diameter (cm)	4.2 (3.9-4.5)	4.2 (4.0-4.8)	0.174
Planimetric MVA (cm ²)	1.8 (1.6-2.0)	1.8 (1.6-1.9)	0.568
MVA PHT (cm ²)	1.8 (1.6-2.0)	1.8 (1.65-2.05)	0.938
Mean gradient (mmHg)	5 (4-6)	6 (5-7)	0.004
Balloon diameter (mm)	28 (28-28)	28 (26-28)	0.254
Balloon inflation			
1 time	24 (18.2)	2 (11.8)	0.569
2 times	84 (63.6)	10 (58.8)	
3 times	22 (16.7)	5 (29.4)	
4 times	2 (1.5)	0 (0)	
Procedural need for emergent surgery	9 (5.7)	0 (0)	-
Severe MR (n, %)	5 (3.2)	0 (0)	-
Tamponade (n, %)	4 (2.5)	0 (0)	-
Emergent intervention			
MVR (n, %)	8 (5.1)	0 (0)	-
Comissurotomy (n, %)	1 (0.6)	0 (0)	-
Procedural success (n, %)	138 (87.9)	17 (81.0)	0.277

TTE: Transthoracic echocardiography, sPAP: Systolic pulmonary artery pressure, LA: Left atrium, MVA: Mitral valve area, PHT: Pressure half time, MR: Mitral regurgitation, MVR: Mitral valve replacement, n: Number
Important p values are written in bold

Table 5. ROC analysis of platelet indices for mitral restenosis

MPV	AUC	95% CI	Cut-off	Sensitivity	Specificity
	0.656	0.541 - 0.770	>9.65	81.0	49.7
PCT	AUC	95% CI	Cut-off	Sensitivity	Specificity
	0.826	0.700 - 0.952	>0.241	76.2	87.9

ROC: Receiver operating characteristic, MPV: Mean platelet volume, PCT: Platelecrit, AUC: Area under curve, CI: Confidence interval

closely related to long-term clinical results of PMBV^(23,24). On this basis, they have hypothesized that complete commissurotomy resulting in larger MVA might prevent fibrous fusion of split commissures and restenosis⁽²⁵⁾. Similar findings were also documented by Ruiz et al.⁽²⁶⁾, they demonstrated that old age, heavy calcification, high WS, and suboptimal opening of mitral valve were major predictive factors for restenosis.

In our study, major predictors of restenosis were high levels of WS, previous history of mitral valve intervention and higher levels of post-procedurally estimated trans-mitral gradient, which were compatible with previous studies. Additionally, we also demonstrated a strong association between higher values of pre-procedural PLT indices, including PLT count, MPV and PCT and rate of restenosis. To the best of our knowledge, this is the first study in literature which revealed a relationship between PLT indices and mitral restenosis.

Evidence from several studies has shown that MPV is a reliable method for measuring PLT size which indicates PLT function. Compared to normal size counterparts, larger PLT has higher hemostatic activity and contributes to the development of increased pro-coagulant activity of PLT, thrombosis and thromboembolism. According to those studies, severe rheumatic mitral stenosis is associated with increased risk for pro-coagulant activity of PLT and thrombosis. The presence of endothelial dysfunction and turbulent blood flow as a result of mitral valve stenosis were possible underlying mechanisms⁽²⁷⁻²⁹⁾. Similar results were demonstrated by Erdogan et al.⁽³⁰⁾ in patients with rheumatic mitral stenosis. According to their study, patients with rheumatic mitral stenosis had a higher MPV than healthy controls [9.05±1.26 vs 7.56±0.74 fl, p<0.001] and those patients had higher PLT activity than controls⁽³⁰⁾. In another study, Chen et al.⁽¹¹⁾ reported increased peripheral venous PLT P-selectin expression in patients with moderate to severe rheumatic mitral stenosis compared to healthy counterparts. They also demonstrated a relationship between the amount of regional left atrial PLT P-selectin expression and the severity of mitral stenosis.

Calculated PCT in a blood sample is known to be an indicator of PLT mass in the blood just as hematocrit which is an indicator of total erythrocyte mass in the blood. Compared to total PLT count, PCT is turned out to be the best parameter in terms of estimating the PLT activity⁽³¹⁾. These findings in these studies demonstrate the close relationship between PLT activity and severity of rheumatic involvement of mitral stenosis.

Apart from above mentioned parameters, our study has also revealed that patients who underwent redo PMBV has a higher incidence of AF, which has been reported as a strong predictor of late outcome in series of balloon and surgical commissurotomy procedures^(32,33). The literature showed the association between increased PLT activation and AF. However, the studies proved that this activation was mostly related to MVA and severity of mitral valve disease⁽³⁴⁾. Therefore, it was suggested that PLT activity, spontaneous echo contrast, mitral valve disease and AF were closely related to each other and AF seemed to be not the cause of increased PLT activity but the severity of mitral valve disease corresponded with the activation⁽³⁵⁾.

Study Limitations

There were several limitations in our study. First, and foremost, the retrospective nature of the study inherently limits the generalizability of our results. Another limitation of our study was relatively a small sample size with a short follow-up time. Although clinical characteristics and immediate post-procedural outcomes of our study were similar to the previous studies, our study population consisted of relatively young patients compared to those studies. Outcomes of this study may not be extrapolated to older patients with less favorable valve characteristics. In addition, we did not assess novel markers of PLT activation status such as soluble P-selectin or soluble CD-40 ligand. Further prospective studies with novel PLT activation markers should be implemented to clarify the relationship between PLT indices and the incidence of mitral restenosis following PMBV.

Conclusion

Estimated WS and post-procedural MVA ($MVA \leq 1.5 \text{ cm}^2$) seem to be still superior than other parameters to predict restenosis after PMBV. However, PLT indices including PLT count, MPV and PCT might be feasible and easy parameters to predict possible restenosis after PMBV.

Ethics

Ethics Committee Approval: This study was approved by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee (decision no: 2020/58, date: 18.08.2020).

Informed Consent: Informed consent was obtained from all patients in accordance with a protocol.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.T., A.A.Ş., Ö.Ç., Design: Ö.T., A.A.Ş., Ö.Ç., Data Collection or Processing: Ö.T., M.D., Analysis or Interpretation: A.A.Ş., M.D., S.K., Literature Search: Ö.T., M.D., Writing: Ö.T., A.A.Ş., M.D., S.K., Ö.Ç.

Conflict of Interest: All authors declare no conflict of interest.

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