



Does the Systemic Immune Inflammation Index and Plasma Atherogenic Index Predict Poor Prognosis in Patients Undergoing Mitral Balloon Valvuloplasty?

Mitral Balon Valvüloplasti Yapılan Hastalarda Sistemik İmmün İnflamasyon İndeksi ve Plazma Aterojenik İndeksi Kötü Prognozu Öngördürür mü?

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ABSTRACT

Objective: In this study, we aimed to investigate the impact of the systemic immune-inflammation index (SII) and plasma atherogenic index (PAI) on adverse outcomes in patients undergoing percutaneous mitral balloon valvuloplasty (PMBV). A 5-year follow-up was conducted in patients with mitral stenosis who underwent PMBV, assessing all-cause mortality, major adverse cardiovascular events (MACE), surgical need for the mitral valve, and requirement for repeat PMBV.

Methods: This single-center retrospective study included 103 patients who underwent PMBV due to rheumatic mitral valve disease between January 2014 and January 2019. Demographic characteristics and pre- and postprocedural echocardiographic data of the patients were analyzed. The 5-year follow-up included assessments of all-cause mortality, MACE, surgical requirement for the mitral valve, and rates of repeat PMBV. Laboratory parameters at admission and at the third-month follow-up were recorded through a review of patient records.

Results: A total of 103 patients (75 females) with a mean age of 41.81±14.83 years were enrolled in the study. At admission, the SII was calculated as 8.49±6.27, PAI as 0.45±0.25, and the mitral valve area (MVA) as 1.16±0.19 cm². Post-procedurally, MVA increased to 1.72±0.23 (p=0.001). At the third-month follow-up, SII was 7.77±7.16, and PAI was 0.47±0.25. While a statistically significant decrease was observed in SII post-procedure (p<0.001), no significant change was noted in PAI (p=0.843). When examining 5-year MACE rates in the deceased group, the SII at admission was 765.5±577.3, and at the third month, it was 794.2±907.6 (p>0.05). Regarding 5-year MACE rates in the deceased group, the PAI value at admission was 0.4±0.41, and at the third month, it was 0.4±0.42 (p>0.05).

Conclusion: In patients undergoing PMBV, SII is a significant parameter indicating a reduction in inflammation. However, both SII and PAI are

Öz

Amaç: Bu çalışmada sistemik immün-inflamasyon indeksi (SII) ve plazma aterojenik indeksinin (PAI) perkütan mitral balon valvüloplasti (PMBV) yapılan hastalarda kötü prognoza olan etkisini araştırmayı amaçladık. PMBV uygulanan mitral darlığı hastalarında 5 yıllık takipte tüm nedenlere bağlı mortalite, majör advers kardiyak olay (MACE), mitral kapağa cerrahi ihtiyacı, tekrar PMBV ihtiyacı değerlendirildi.

Yöntemler: Tek merkezli, retrospektif olan çalışmamız Ocak 2014 ve Ocak 2019 tarihleri arasında romatizmal mitral darlık nedeniyle PMBV uygulanan 103 hastayı içermektedir. Hastaların demografik özellikleri, işlem öncesi ve sonrası ekokardiyografik verileri incelendi. Hastaların 5 yıllık tüm nedenlere bağlı mortalite, MACE, mitral kapağa cerrahi ihtiyacı, tekrar PMBV oranlarına bakıldı. Hasta kayıtları üzerinden yapılan taramada başvuruda ve üçüncü ay kontrolde bakılan laboratuvar parametreleri kaydedildi.

Bulgular: Yaş ortalaması 41,81±14,83 yıl olan 103 hasta (75 kadın) çalışmaya dahil edildi. Başvuruda SII 8,49±6,27, PAI 0,45±0,25 ve mitral kapak alanı (MVA) 1,16±0,19 cm² olarak hesaplandı. İşlem sonrası MVA 1,72±0,23 idi (p=0,001). İşlem sonrası üçüncü ayda SII 7,77±7,16 ve PAI 0,47±0,25 olarak hesaplandı. İşlem sonrası SII'de istatistiksel olarak anlamlı bir düşüş gözlenirken (p<0,001), PAI'de anlamlı bir değişiklik gözlenmedi (p=0,843). Beş yıllık MACE oranlarına bakıldığında mortal olan grupta başvuru anındaki SII 765,5±577,3, üçüncü aydaki SII 794,2±907,6 (p>0,05) olarak hesaplandı. Yine mortal olan grupta başvuru anındaki PAI değeri 0,4±0,41, üçüncü aydaki PAI 0,4±0,42 (p>0,05) olarak hesaplandı.

Sonuç: MBVP yapılan hastalarda SII inflamasyondaki azalmayı göstermesi açısından önemli bir parametredir. Ancak SII ve PAI, MBVP yapılan hastalarda 5 yıllık MACE sıklığını göstermesi açısından yetersizdir. Kötü prognozun gösterilmesi açısından ilave parametrelere ihtiyaç duyulmaktadır.

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Received/Geliş Tarihi: 19.09.2023

Accepted/Kabul Tarihi: 2.05.2024



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ABSTRACT

insufficient for predicting the 5-year MACE frequency after PMBV. Additional parameters are required to indicate poor prognosis.

Keywords: Percutaneous mitral balloon valvuloplasty, mitral valve stenosis, systemic immune-inflammation index, plasma atherogenic index, MACE

Öz

Anahtar Sözcükler: Perkütan mitral balon valvüloplasti, mitral kapak darlığı, sistemik immün-inflamasyon indeksi, plazma aterosjenik indeks, MACE

INTRODUCTION

While the incidence of rheumatic heart disease has declined, rheumatic mitral valve stenosis (MS) remains a significant contributor to mortality and morbidity, particularly in developing countries. Percutaneous mitral balloon valvuloplasty (PMBV) is the preferred treatment for severely symptomatic patients. However, there is a notable lack of sufficient data regarding the long-term follow-up outcomes for individuals who have undergone PMBV. Procedural success is influenced by factors such as young age and favorable valve anatomy. Additionally, emerging evidence suggests that clinical outcomes post-PMBV depend not only on mitral valve anatomy but also on various clinical features (1). It has been established that chronic inflammation persists following rheumatic involvement. Recent studies investigating the presence of inflammation have identified new biomarkers such as the platelet-lymphocyte ratio, neutrophil-lymphocyte ratio, systemic immune-inflammatory index (SII), and plasma atherogenic index (PAI). SII has demonstrated predictive value for mortality in patients with conditions like hypertension, diabetes, and coronary artery disease (CAD). These biomarkers serve as indicators of inflammation and immune response, offering valuable insights into the ongoing inflammatory processes. Their relevance extends beyond rheumatic involvement, contributing to prognostic assessments in various medical conditions, including those mentioned earlier (2-4). Elevated SII levels before TAVI have demonstrated predictive value for major adverse cardiac events (MACE) and short-term mortality. This finding underscores the potential utility of SII as a prognostic marker in the context of TAVI, providing valuable insights into risk assessment for adverse cardiac events and mortality in the immediate post-procedural period (5). PAI is an index proposed by Dobiášová and Frohlich (6) in 2000. It is calculated as the logarithmic transformation of the triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) to base 10 (6). It influences the prognosis following percutaneous coronary intervention in patients with type 2 diabetes (7). In this study, our objective was to assess the prognostic impact of the SII and PAI on all-cause mortality, MACE, and the need for mitral valve surgery or repeat PMBV at the 5-year follow-up after PMBV.

MATERIALS AND METHODS

Our single-center, retrospective study included 103 patients who underwent mitral balloon valvuloplasty for rheumatic mitral stenosis between January 2014 and January 2019. Patients with known inflammatory disease, autoimmune disorders, chronic liver disease, malignancy, valve diseases requiring intervention other than mitral valve disease, presence of thrombus in the left atrium or atrial appendage, and active infections were excluded from the study. The demographic and medical characteristics of

the patients were extracted from their medical records and the hospital's digital recording system. Routine laboratory parameters were assessed before the PMBV procedure and during the 3-month follow-up post-procedure, and the results were documented. In the echocardiography conducted prior to the procedure, measurements included the maximum and minimum gradients of the valve, valve area, Wilkins score, left atrium size, degrees of mitral and tricuspid regurgitation, and pulmonary artery pressure values. Post-procedure, the recorded parameters encompassed valve gradients, valve area, degrees of mitral and tricuspid regurgitation, and changes in pulmonary artery pressure. The SII was calculated using the neutrophil x platelet/lymphocyte formula (8); PAI was determined as the logarithm of the ratio of TG/HDL, calculated to the base 10 (6). Patients were assessed for all-cause mortality, MACE, necessity for mitral surgery, and recurrence of PMBV within a 5-year period following the procedure. Efforts were made to contact patients for whom information could not be accessed, using phone numbers registered in the hospital system. Patients with incomplete information during file review and those whose data could not be retrieved were excluded from the study.

This study was conducted in adherence to the Principles of the Declaration of Helsinki. Ethical approval was obtained from our Faculty's Clinical Research Ethics Committee (approval number: 3742, date: 15.04.2022).

Statistical Analysis

The research data were analyzed using SPSS 20.0. Descriptive statistics, such as average values for quantitative variables and the number of cases (percentage) for qualitative variables, were employed to present the results of the study based on the distribution of the data. Student's t-test for independent groups was used in normally distributed data for comparisons between two groups. In cases where the assumption of normality was not met among dependent groups, the Friedman test was employed for mean comparisons. For groups exhibiting non-normal distribution, the Kruskal-Wallis test was applied to assess the significance of differences among the averages of three or more groups. In all statistical tests, a p-value of 0.05 was considered statistically significant.

RESULTS

A total of 103 patients, including 75 women, with an average age of 41.81 ± 14.83 years were enrolled in the study. Among the patients, 9.9% (n=10) had diabetes and 19.8% (n=20) had hypertension. Atrial fibrillation was identified in 44.5% (n=46) of the patients through electrocardiographic evaluation before the procedure (Table 1). The ejection fraction of the study participants was 59.08 ± 3.19 , and the Wilkins score was 8.42 ± 0.93 . The balloon size employed was

27.5±1.16 mm. In the echocardiographic assessment before the procedure, the maximum gradient was computed as 22.31±6.19, the mean gradient was 11.96±4.18, and the mitral valve area was determined as 1.12±0.26. Post-procedurally, a statistically significant decrease in the maximum and mean gradients in the valve area [(12.25±3.52; p<0.001), (5.76±1.88; p<0.001), (1.93±0.25; p<0.001)] was observed (Table 2). While the mean pulmonary artery pressure was 44.81±12.12 before the procedure, it decreased to 36.75±8.3 after the procedure (p<0.001). Although a statistically significant reduction in the SII was noted at the third-month follow-up [(852.176±631.896 vs. 772.9±714.68; p=0.009)], no significant change was observed in the PAI [(0.422±0.413 vs. 0.455±0.415; p=0.680)] (Table 3). When considering the 5-year MACE rates, in the mortality group, the SII at the time of admission was calculated as 765.5±577.3, and the SII at the third month was calculated as 794.2±907.6 (p>0.05). Similarly, in the mortality group, the PAI value at the time of admission was calculated as 0.4±0.41, and the PAI at the third month was calculated as 0.4±0.42 (p>0.05) (Table 4).

DISCUSSION

In the aftermath of acute rheumatic fever (ARF), autoantibodies activate complement proteins in susceptible individuals, initiating an inflammatory process that leads to cardiac damage. This inflammation affects all layers of the heart, with a particularly severe effect on valves originating from the endocardium. Although the inflammatory process affects all valves, it is notably more pronounced in the mitral valve. Chronic inflammation persists for years following an acute attack. In both ARF and chronic rheumatic valve patients, intralesional mononuclear cells predominantly secrete interferon, tumor necrosis factor (TNF), and Th1-type cytokines (9). This suggests that even during the chronic phase, these mononuclear

Table 1. Demographic data of the patients

Variables	Before mitral balloon valvuloplasty
Female (n, %)	75 (75.2)
Age (mean ± SD)	41.81±14.83
DM (n, %)	10 (9.9)
HT (n, %)	20 (19.8)
COPD (n, %)	2 (1.9)
CKD (n, %)	4 (3.8)
AF (n, %)	46 (44.5)

DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, AF: Atrial fibrillation, SD: Standard deviation.

Table 2. Comparison of echocardiographic data of the study group before and after PMBV

Variables	Before PMBV	After PMBV	P-value
Maximum gradient (mmHg)	22.31±6.19	12.25±3.52	<0.001
Mean gradient (mmHg)	11.96±4.18	5.76±1.88	<0.001
PAP (mmHg)	44.81±12.12	36.75±8.3	<0.001
MVA (cm ²)	1.12±0.26	1.93±0.25	<0.001

PAP: Pulmonary artery pressure MVA: Mitral valve area, PMBV: Percutaneous mitral balloon valvuloplasty.

cells continue to produce inflammatory cytokines. Previous studies have indicated that the levels of chronic inflammatory markers in patients with rheumatic valve disease are elevated compared with those in control groups (6). C-reactive protein (CRP) is a well-established marker of inflammation. The CRP levels were notably higher in the chronic rheumatic valve disease group than in the control group (10). Another study revealed a correlation between CRP levels, Wilkins score, and the severity of valve involvement (11). This finding represents additional evidence of ongoing inflammation. In patients with chronic rheumatic valve disease, inflammatory markers such as interleukin-6 (IL-6), IL-2, IL-8, TNF-alpha, fibrinogen, and CRP have been reported to exhibit a strong association with

Table 3. Laboratory values of the patients before the procedure and at the 3rd month of follow-up

Variables	Before PMBV	After PMBV	P-value
WBC (10 ³ /u/L)	8,261±2,659	8,340±2,654	0.831
NEU (10 ³ /u/L)	5,483±2,396	5,337±2,363	0.666
LYM (10 ³ /u/L)	1,956±0.876	2,193±0.926	0.02
HGB (g/dL)	15,270±15,801	14,471±9,614	0.163
PLT (10 ³ /u/L)	255.02±76,861	258.94±88,963	0.686
MO (10 ³ /u/L)	0.471±0.487	0.516±0.231	0.516
SII	852,176±631,896	772.9±714.68	0.009
GFR (mL/dk)	89.51±16.72	88,505±17.18	0.793
BUN	33,643±14,352	35,676±26.29	0.149
CRE (mg/dL)	1.03±0.401	0.965±0.444	<0.001
NA (mmol/L)	138.52±2,336	139.01±2,252	0.055
K (mmol/L)	4,382±0.615	4,355±0.468	0.806
CA (mg/dL)	9.6±0.565	8.6±1,414	0.157
LDL (mg/dL)	112.43±35,774	105,637±35.00	0.230
TG (mg/dL)	143,315±74,662	147.99±86,669	0.920
HDL (mg/dL)	44,538±10,605	44,431±10,141	0.473
T. col (mg/dL)	183,295±44.00	175,171±43,456	0.423
PAI	0.422 ± 0.413	0.455 ± 0.415	0.680

WBC: White blood cell, NEU: Neutrophil, LYM: Lymphocyte, PLT: Platelet, GFR: Glomerular filtration rate, BUN: Blood urea nitrogen, CRE: Creatinin, NA: Sodium K: Potassium CA: Calcium, T. col: Total cholesterol, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SII: Systemic immun inflammation index, PAI: Plasma atherogenic index.

Table 4. Relationship between pre-PMBV and 3rd month control SII and PAI values and 5-year MACE

Variables	MACE (+)	MACE (-)	P	T
SII (before the procedure)	765.7±577.3	897.7±655.4	0.304	1.034
SII (third month)	794.2±907.6	767.4±551.9	0.857	-0.180
PAI (before the procedure)	0.4±0.41	0.42±0.41	0.784	0.274
PAI (third month)	0.4±0.42	0.49±0.41	0.317	1.006

PMBV: Percutaneous mitral balloon valvuloplasty, SII: Systemic immun inflammation index, PAI: Plasma atherogenic index, MACE: Major adverse cardiovascular events.

the severity of valve involvement. Furthermore, these markers are linked to valve calcification and deterioration according to the New York Heart Association (NYHA) class (12).

Despite technological advancements, the Wilkins score remains a crucial tool for effectively selecting candidates for PMBV. In its early years, PMBV was primarily administered to patients with low Wilkins scores, aligning with favorable acute outcomes. However, as technical expertise developed and experience increased, indications expanded to encompass patients with intermediate scores (13). Clinical outcomes after PMBV have been documented to depend on various factors, in addition to mitral valve anatomy (14,15). The key determinants influencing long-term outcomes after successful PMBV include suboptimal valve patency, age, and prior unfavorable NYHA functional class (1). The SII is a marker of systemic inflammation calculated using the formula neutrophil platelet/lymphocyte. Elevated SII values correlate with adverse outcomes and increased MACE rates in patients with severe aortic stenosis undergoing TAVI (5). In another study, it was reported that the incidence of contrast-mediated nephropathy after TAVI was higher in the group with elevated SII (16). We observed a statistically significant decrease in SII values in the 3rd month following successful PMBV compared with pre-procedure levels. This reduction may be attributed to the decrease in inflammation resulting from the reduction in increased left atrial pressure after PMBV. Throughout the 5-year follow-up, the primary endpoints of the study, including all-cause mortality, MACE, the need for mitral valve surgery, and repeat PMBV, were not found to be correlated with the pre-procedure and 3-month control SII values.

Another aspect to consider is the role of inflammatory mechanisms in the progression of CAD and atheroma formation. Dyslipidemia stands out as one of the most critical factors contributing to CAD. Low-density lipoprotein cholesterol has been demonstrated to be highly susceptible to oxidative damage, consequently promoting the development of atherosclerotic lesions (17). Elevated PAI, calculated as the logarithmic transformation of the ratio of TG/HDL-C to the base 10, has been linked to an increased risk of atherosclerosis and coronary heart disease (18,19). PAI has been demonstrated to exhibit a correlation with CAD severity, and it also predicts MACE over a 3-year period, even in the absence of traditional risk factors (20). Although there is no established clear-cut threshold indicating high risk, PAI levels were observed to be <0.1 in umbilical cord samples, young children, and healthy women. Conversely, values up to 0.4 were identified in individuals with high atherosclerotic risk factors (19). In various studies, a PAI level <0.1 was categorized as low risk, 0.1-0.24 was deemed intermediate risk, and >0.24 was classified as high risk (17-19). In a separate study, a PAI level <0.11 was categorized as low risk, 0.11-0.21 was designated as medium risk, and >0.21 was identified as high risk (21). A robust association has been demonstrated between the development and severity of mitral annular calcification (MAC) and PAI (22). Considering the evident impact of inflammation on atheroma formation and the established role of PAI as a predictor of atherosclerosis, we investigated the variations in PAI values before and after PMBV in patients with mitral stenosis. The mean PAI value for patients with mitral stenosis before the procedure was determined as 0.422 ± 0.413 . This value exceeded the literature's threshold, indicating a high risk of CAD (17-19,21). The PAI value

measured in the third month after the procedure did not exhibit a significant difference from the pre-procedure value. This may be attributed to the prolonged impact of lipid metabolism. Given the relatively short duration of our study, it is plausible that no disparity was observed in the results. It is evident that a longer follow-up period is essential for a comprehensive evaluation of effectiveness. PAI values measured before PMBV and at 3 months were not identified as effective markers in predicting MACE in the 5-year follow-up.

Study Limitations

The limitations of our study include its retrospective design with a small number of patients and incomplete documentation of the short- and long-term anti-inflammatory drugs used by the patients during the follow-up period.

CONCLUSION

The data obtained support the persistence of a chronic inflammatory response in patients with rheumatic mitral stenosis, consistent with existing studies in the literature. While the ability of the SII to indicate a reduction in inflammation in patients undergoing PMBV is noteworthy, both SII and PAI are insufficient in predicting the 5-year frequency of MACE. Additional parameters need to be evaluated for an accurate determination of poor prognosis.

Ethics

Ethics Committee Approval: Ethical approval was obtained from our Faculty's Clinical Research Ethics Committee (approval number: 3742, date: 15.04.2022).

Informed Consent: Retrospective study.

Author Contributions

Concept: S.T., Design: N.A., Supervision: A.T.Ş., Resources: Y.A., Materials: N.A., Data Collection or Processing: A.T.Ş., Analysis or Interpretation: S.T., Literature Search: Y.A., Writing: N.A., Critical Review: S.T.

Conflict of Interest: No conflict of interest is declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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