

# Systemic Immune Inflammation-Index and CANLPH Score in Patients with Mitral Stenosis Undergoing Balloon Valvuloplasty

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## ABSTRACT

**Objective:** to evaluate CANLPH score and systemic immune inflammation index (SII) in patients with symptomatic rheumatic mitral stenosis (MS) undergoing percutaneous mitral balloon valvuloplasty (PMBV).

**Methods:** 62 patients who underwent PMBV in our clinic between 2018 and 2021 were included retrospectively. The patients were divided into 2 groups according to echo score. The CANLPH score was calculated from the cut-off values of C-reactive protein to albumin ratio (CAR), neutrophil to lymphocyte ratio (NLR) and platelet to hemoglobin ratio (PHR), determined with the Youden index and SII by the formula  $\text{platelet} \times \text{neutrophil} / \text{lymphocyte}$ .  $P < 0.05$  was considered statistically significant.

**Results:** The mean age of the patients was  $44.5 \pm 10.4$  years (40 female, 64.5%). The mean values of SII and CANLPH scores were higher in the Echo score  $> 8$  group ( $p < 0.001$ , both). The mean mitral gradient before and after PMBV was  $12.6 \pm 5.7$  mm Hg and  $5.0 \pm 2.4$  mm Hg, and the mean valve area was  $1.12 \pm 0.27$  cm<sup>2</sup> and  $1.85 \pm 0.29$  cm<sup>2</sup>. A statistically significant and negative correlation was observed between the gradient decrease after the procedure and the CANLPH score and SII ( $r = -0.426$ ,  $p = 0.001$  and  $r = -0.418$ ,  $p = 0.001$ , respectively). In receiver operating characteristic (ROC) curve analysis, it was concluded that the ability of CANLPH score to predict the higher Echo scores was noninferior to SII with an area under curve (AUC:0.820 (0.701-0.906) and AUC:0.786 (0.664-0.880), z statistics 0.576 and  $p = 0.564$ .

**Conclusion:** SII and CANLPH scores are correlated with Echo score. A significant negative relationship was found with both biomarkers and gradient decrease after the PMBV.

**Keywords:** CANLPH score, mitral stenosis, percutaneous balloon valvuloplasty, systemic immune-inflammation index

## INTRODUCTION

The most important cause of mitral stenosis is rheumatic carditis, and isolated mitral stenosis is seen in 40% of patients with carditis.<sup>1</sup> The time until symptoms develop is long, and symptoms increase gradually in 50% of patients.<sup>2</sup> Procedure is necessary in symptomatic patients and if the valve anatomy is suitable, percutaneous balloon valvuloplasty (PMBV) is the first choice.<sup>3</sup>

The plasma levels of cytokines and chemokines such as interleukin-1 (IL-1), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), interleukin-6 (IL-6) and interleukin-12 (IL-12) to decrease after PMBV indicates the link between inflammation and severity of mitral stenosis.<sup>4</sup> There are also studies supporting that high neutrophil to lymphocyte ratio (NLR) values are associated with severity of mitral stenosis.<sup>5</sup>

The systemic immune-inflammation index (SII) and CANLPH score can be used to evaluate the host's current degree of inflammation.<sup>6,7</sup> Both have prognostic importance for many clinical situations.<sup>8,9</sup> The SII can predict prognosis and survival after coronary artery disease and mortality in patients with infective endocarditis.<sup>10</sup> Tosu et al. determined that SII could predict short-term mortality in patients with aortic stenosis who underwent transcatheter aortic valve implantation.<sup>11</sup> CANLPH score is a prognostic biomarker especially used in malignancy.<sup>12</sup> In a recently published study, it has been mentioned that the CANLPH score can be used to determine mortality after coronary artery bypass grafting.<sup>13</sup> This result was based on the thesis that the inflammatory process is involved in most of the mortality and complications in coronary artery disease. The aim of this study is to evaluate CANLPH score and SII in patients who underwent PMBV

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and the relationship between echo score and gradient decrease after balloon valvuloplasty and inflammatory markers.

## METHODS

### Study Population and Laboratory Measurements

Sixty-five patients with mitral stenosis that had been treated with PMBV in our clinic between January 2018 and December 2020 were included in this retrospective study. Three patients, two had atrial fibrillation and one patient who was taken to emergency surgery after the development of pericardial tamponade during the procedure, were excluded. Patients with a history of transischemic attack or cerebrovascular disease, with known inflammatory disease, autoimmune disease, or chronic liver disease, malignancy, valvular disease requiring procedures other than mitral stenosis, presence of thrombus in the left atrium or atrial appendage, active infection were also excluded. The demographic and medical characteristics of the patients were obtained from their files and in the hospital digital recording system. Routine laboratory parameters of the patients were examined before PMBV procedure and were recorded in the hospital digital system. C-reactive protein to albumin ratio (CAR), neutrophil to lymphocyte ratio (NLR) and platelet to hemoglobin ratio (PHR) are all associated with the systemic inflammatory status of the host and the CANLPH score, a combination of these three markers, was calculated from the cut-off values of CAR, NLR and PHR determined with the Youden index. SII was calculated by the formula platelet X neutrophil/ lymphocyte.<sup>12</sup>

Hypertension was defined as a systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, or current use of antihypertensive medication. Diabetes mellitus was defined as fasting serum glucose  $\geq 126$  mg/dL, hemoglobin A1c  $\geq 6.5\%$ , or the use of blood glucose lowering agents

A successful procedure was defined as an increase in the valve area above  $1.5 \text{ cm}^2$  and the degree of mitral regurgitation less than severe.

The study was approved by the local Clinical Research Ethics Committee of our hospital (2.6.2021, 1432). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

#### Main Points:

- Mitral stenosis is an inflammatory process and it has been shown that inflammation regresses after treatment.
- CRP, SII and CANLPH are biomarkers of host's inflammatory status and all of them were higher in the patients with mitral stenosis with higher Echo scores.
- The decrease in mean gradient after balloon valvuloplasty was associated and moderately correlated with both SII and CANLPH.

### Transthoracic and Transesophageal Echocardiography

Transthoracic and transesophageal echocardiography (TTE-TOE) were performed using commercially available ultrasonographic equipment according to recommendations of the American Society of Echocardiography before the procedure and TTE after the procedure.<sup>14</sup> TTE examinations included M-mode, two dimensional and Doppler flow imaging measurements. Left ventricular ejection fraction was measured and recorded using the modified biplane Simpson method. The transmitral mean gradient assessed by means of tracing mitral inflow was calculated and mitral valve area with the direct planimetry of the orifice in the parasternal short-axis view was performed. After calculating the mean gradients before and after the procedure, the difference was expressed as percentage. Systolic pulmonary artery pressure was determined according to formula  $(4 \times [\text{peak TR velocity}]^2) + \text{RA pressure}$  where TR is tricuspid regurgitation and RA is the right atrium. Echo score of Wilkins was used to classify the patients into two groups according to echo score of 8 or less and higher than 8. TOE was performed to rule out left atrial and appendage thrombi.

### Statistical Analysis

All statistical analysis were performed with SPSS 17 (SPSS, Inc. Chicago, Illinois, USA) and MedCalc (v19.6.1) for Windows. Continuous variables were expressed as mean  $\pm$  standard deviation (mean  $\pm$  SD) or median (interquartile range) and categorical variables as numbers and percentages. Comparisons of the continuous variables between groups were performed using the independent samples t-test and Mann-Whitney U test, as appropriate and categorical variables using the  $\chi^2$  test or Fisher's Exact test. Whether continuous variables have normal distribution was analyzed with Kolmogorow-Smirnov test. Univariate and multivariable logistic regression analyses were performed to assess the relationship between the CANLPH score and SII and mitral stenosis. Variables with a p value  $\leq 0.05$  in univariate analysis were included in the multivariate analysis. Receiver operating characteristic (ROC) curve analysis was performed to demonstrate the cut-off values and sensitivity and specificity of SII and CANLPH score in showing the MS severity. The results are expressed as relative risk and 95% confidence interval (CI). A p value less than 0.05 was considered as statistically significant.

## RESULTS

The mean age of the patients was  $44.5 \pm 0.4$  (40 female, 64.5%). Of the 27 patients in the group with an echo score of 8 and below, 16 were female; while 24 of the 35 patients in the group with an echo score above 8, were female. The average of the echo scores was  $4.5 \pm 1.1$  and  $9.1 \pm 0.9$ , respectively. When the demographic characteristics of the patients were compared, it was found that the groups were similar in terms of diabetes mellitus, hypertension, gender, age and ejection fraction ( $p=0.626$ ,  $p=0.715$ ,  $p=0.447$ ,  $p=0.089$  and  $p=0.803$ , respectively). Baseline demographic characteristics, laboratory results and echocardiographic findings of groups are summarized in Table 1. The only laboratory parameter that the difference was significant between the groups was C-reactive protein (CRP) ( $p=0.042$ ).

**Table 1- Clinical, echocardiographic and laboratory data of the study population**

Variables	Echo score ≤8, n=27	Echo score >8, n=35	p
Age, years	42±9	46±11	0.089
Female, n(%)	16 (59.2)	24(68.5)	0.447
HT, n(%)	6(22.2)	9(25.7)	0.715
DM, n(%)	4(14.8)	6(17.1)	0.626
EF,%	59±4	60±3	0.803
Echo score	4.5±1.1	9.1±0.9	<0.001
Pre-PMBV mean gradient, mm Hg	12.5±5.8	12.7±5.7	0.895
Pre-PMBV MVA, cm <sup>2</sup>	1.0±0.2	1.1±0.3	0.376
Post-PMBV mean gradient, mm Hg	4.6±1.6	5.3±3.0	0.285
Post-PMBV MVA, cm <sup>2</sup>	1.8±0.2	1.8±0.3	0.689
SPAP, mm Hg	44.6±13.4	48.6±15.4	0.512
Δ mean gradient post-PMBV, %	61.4±14.3	52.3±16.4	0.035
CRP, mg/L	3.0±2.6	4.6±3.3	0.042
Albumin, g/dL	4.1±0.3	4.0±0.4	0.604
Neutrophil, 10 <sup>3</sup> /μl	4.6±1.8	5.4±1.4	0.055
Lymphocyte, 10 <sup>3</sup> /μl	2.1±0.7	1.9±0.5	0.112
PLT, 10 <sup>3</sup> /μl	229.6±68.3	236.2±50.3	0.662
HG, g/dL	12.9±1.7	13.0±1.6	0.752
WBC, 10 <sup>3</sup> /μl	7.5±2.0	8.2±1.7	0.136
MPV, fL	9.8±1.2	9.7±1.2	0.962
RDW, %	14.7±2.1	14.7±1.7	0.707
Glucose, mg/dL	92.0±18.0	110.2±31.8	0.059
Creatinine, mg/dL	0.6±0.1	0.7±0.1	0.166
Uric acid, mg/dL	4.9±1.1	5.6±1.7	0.250
Triglyceride, mg/dL	140.2±101.5	151.2±87.1	0.538
LDL, mg/dL	126.7±28.9	136.5±34.8	0.284
CAR	0.7±0.6	1.0±0.6	0.036
NLR	2.2±1.1	3.0±1.3	0.014
PHR	18.0±5.9	18.2±4.5	0.872
SII	463.2±159.5	689.6±238.4	<0.001
CANLPH	0.9±0.6	2.0±0.9	<0.001

HT: hypertension, DM: diabetes mellitus, EF: ejection fraction, PMBV: percutaneous mitral baloon valvuloplasty, MVA: mitral valve area, SPAP: systolic pulmonary artery pressure, CRP: C-reactive protein, PLT: platelets, HG: hemoglobin, WBC: white blood cell count, MPV: mean platelet volume, RDW: red cell distribution wide: LDL: low density lipoprotein cholesterol, CAR: CRP/ albumin ratio, NLR: neutrophil/lymphocyte ratio, PHR: platelet/hemoglobin ratio, SII: systemic immune inflammation index, CANLPH: CRP/albumin, neutrophil/lymphocyte, platelet/hemoglobin

When the echocardiographic records of the groups were compared, no significant difference was found between the mean gradient, mitral valve area and pulmonary artery systolic pressure before the procedure ( $p=0.895$ ,  $p=0.376$  and  $p=0.512$ , respectively). Although the mean gradient, and mitral valve area were similar between the groups after percutaneous balloon valvuloplasty, the percentage decrease in the mean gradient was statistically significantly lower in the group with an echo score above 8 compared to the other group ( $p=0.285$ ,  $p=0.689$  and  $p=0.035$ , respectively).

The mean CAR, NLR, SII and CANLPH score were higher in the group with echo score  $>8$  ( $p=0.036$ ,  $p=0.014$ ,  $p<0.001$  and  $p<0.001$  respectively) although mean PHR was similar ( $p=0.872$ ). When the cut-off values of PHR, CAR and NLR were calculated using the Youden index; the cut-off value for PHR was 16.18 (sensitivity 71.4%, specificity 48.1%); 0.84 for CAR (sensitivity 62.9%, specificity 76.9%) and 2.37 for NLR (sensitivity 80%, spec-

ificity 70.4%). The cut-off value of SII for the higher echo score group was  $>667.79$  with a sensitivity of 57.1% and specificity of 96.3% while  $>1$  with a sensitivity of 77.1% and specificity of 81.4 for CANLPH score. Although female sex was dominant in both group; SII and CANLPH score and the decrease in percentage in mean gradient after the procedure were similar between females and males ( $p=0.324$ ,  $p=0.414$  and  $p=0.314$ , respectively).

When the relationship of CRP, CAR, NLR, SII and CANLPH scores with the echo score was evaluated, it was seen that all biomarkers were positively correlated with the echo score and the correlation coefficient determining the relationship with the CANLPH score was higher than the others. The results of the correlations between inflammatory markers and echo score and gradient decrease after the procedure are shown in Table 2. The best correlation with the gradient decrease (in percentage) after the procedure was again with the CANLPH score and was in the opposite direction (Figure 1-4).

**Table 2-** Correlations between Echo score,  $\Delta$  mean gradient post-PMBV % and SII, CAR, NLR and CANLPH

Variables	r	p
CRP- Echo score	0.251	0.049
CAR-Echo score	0.256	0.047
NLR-Echo score	0.390	0.002
SII- Echo score	0.562	$<0.001$
CANLPH- Echo score	0.602	$<0.001$
$\Delta$ mean gradient postPMBV,% - CRP	-0.084	0.544
$\Delta$ mean gradient postPMBV,% -CAR	-0.304	0.025
$\Delta$ mean gradient postPMBV,% -NLR	-0.279	0.039
$\Delta$ mean gradient postPMBV,% - SII	-0.418	0.001
$\Delta$ mean gradient postPMBV,% - CANLPH	-0.426	0.001

CRP: C-reactive protein, CAR: CRP/albumin ratio, NLR: neutrophil/lymphocyte ratio, SII: systemic immune inflammation index, CANLPH: CRP/albumin, neutrophil/lymphocyte, platelet/hemoglobin, PMBV: percutaneous mitral baloon valvuloplasty

Figure 1- Correlation of Echo score and CANLPH score

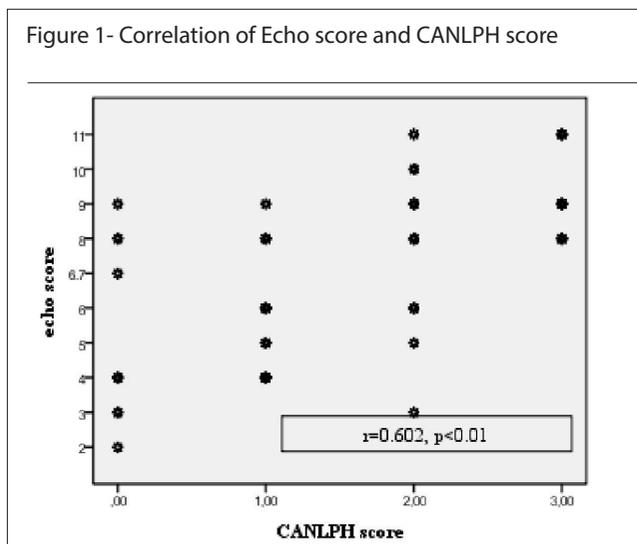
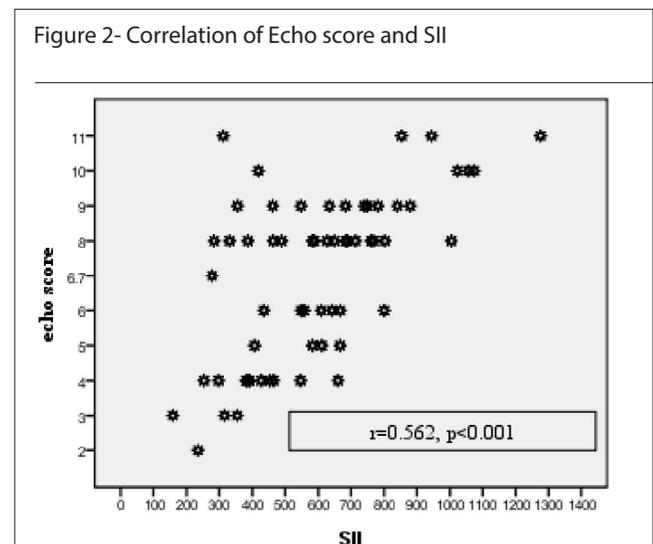
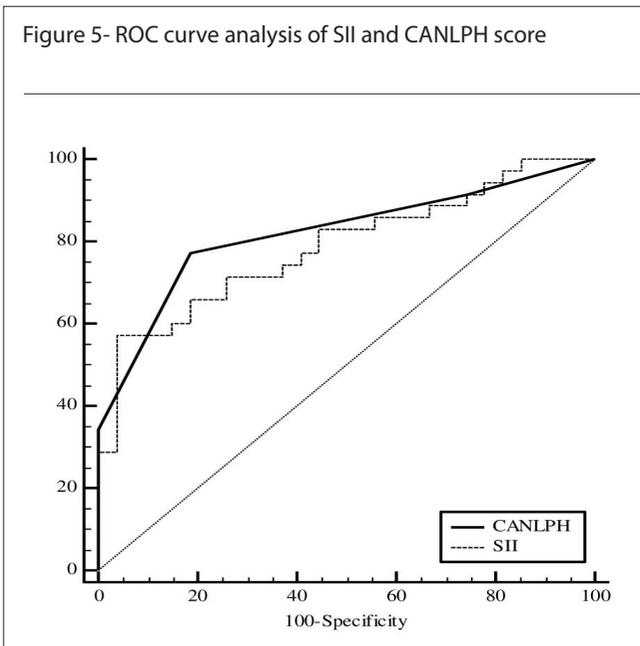
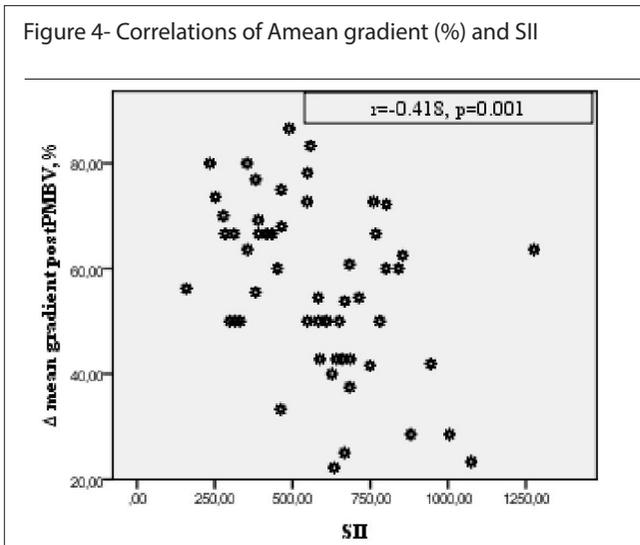
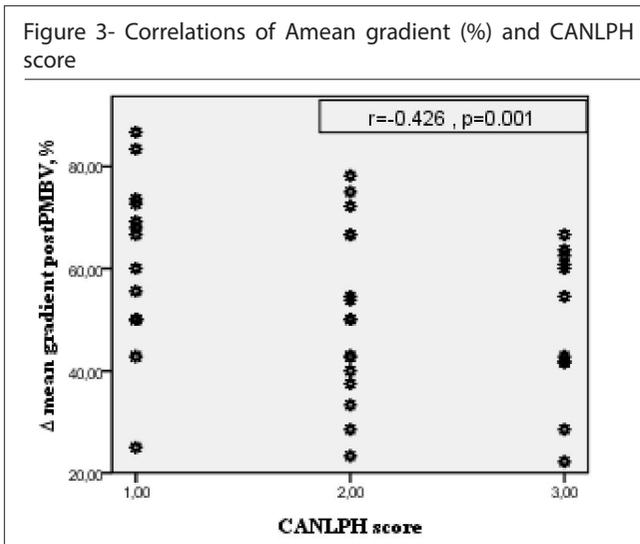


Figure 2- Correlation of Echo score and SII





Pairwise comparison of ROC curve analysis for determining the predictive value of higher Echo scores revealed that the CANLPH score was noninferior to SII with an AUC: 0.820 (0.701-0.906) and AUC: 0.786 (0.664-0.880), difference between AUC:0.034, z statistics 0.576 and p=0.564 (Figure 5).

**DISCUSSION**

The main results of this study were: 1) the increase in Echo score was correlated with the increase in inflammatory biomarkers such as CRP, NLR, and CAR, 2) new markers as SII and CANLPH score were also associated with the Echo score, 3) the relationship between the CANLPH score and the MS echo score was further, and this result is also provided by the relation of mitral mean gradient decrease after PMBV, 4) Our study was the first to consider the SII and CANLPH scores in patients with symptomatic MS with PMBV indication, and showed that they are related with the Echo score and the success of the procedure.

There are many factors that affect the success of PMBV. These parameters include age, sex, echo score, presence of atrial fibrillation, right heart function and degree of pulmonary artery pressure, and biomarkers that determine the host's inflammation status, such as the NLR in recent studies.<sup>15,16</sup> Krishnamoorthy and Dash suggested that advancing age reduces the immediate and late recovery of atrial contribution after MBV and younger patients, especially below 18, achieve better atrial filling.<sup>17</sup> Most of the patients in our study were in their 40s. Therefore, it is possible to state that the probability of a complete recovery in atrial function in long-term follow-up is low compared to these data. It is controversial whether gender has a positive or negative effect on the success of the procedure.<sup>18,19</sup> Although female gender was dominant in the patients in our study group; no gender-related differences were observed in echo score, SII and CANLPH score, or post-procedure gradient decrease. The echo score is considered to be the most important factor in the success of the procedure. In the chronic inflammatory process, proliferation and fibrosis formation are observed due to the increase of lymphocytes and fibroblasts in the valvular tissue. This factor, which affects the success of the percutaneous balloon procedure, is also directly related to the level of inflammation. There are many studies stating that success is low in patients with the score over 8, considering the components of the echo MV score. In the study of Ekinci et al., it was shown that the success rate was high in patients with echo scores between 9 and 11.<sup>20</sup> Mahfouz et al. also emphasized that the global echo-Doppler score correlated better with the success of the procedure than the classical echo score.<sup>21</sup> In our study, successful application was also performed in patients with echo scores between 9 and 11. The presence of atrial fibrillation shows that the severity of MS is increased and the inflammation process is accelerated, and it has a negative effect on the success of the valvuloplasty. Since inflammatory markers were considered in this study, patients with atrial fibrillation were excluded in terms of possible bias. The increased pulmonary artery pressure before valvuloplasty is important both because it is an indicator of increased right ventricular afterload and has effect on the success of the procedure and the outcomes after the procedure. Studies have shown that performing valvuloplasty before pulmonary hypertension develops is more ap-

appropriate for preserving right ventricular functions.<sup>22,23</sup> Mean systolic arterial pressure in our patient group was over 40. Since we do not have long-term results, it is not possible to interpret how the increased pulmonary arterial pressure plays a role in the post-procedure clinic. We can only say that there was no negative effect on the success of the procedure, at least in the acute period.

Valvular diseases, especially rheumatic mitral stenosis and calcific aortic stenosis, are among the cardiac pathologies in which inflammation is detected most intensely. Erdogan and colleagues showed that SII is related to valve area and transaortic mean gradient in aortic stenosis. In both rheumatic mitral stenosis and calcific aortic stenosis, a decrease in the inflammation level of the host was observed after treatment. Furthermore, it is known that plasma levels of many inflammatory cytokines decrease after PMBV. These data support that the severity of MS is related to the inflammatory state. The NLR is one of these parameters, and studies show that it correlates well with the severity of the MS.<sup>24</sup> SII and CANLPH score are biomarkers that reflect systemic inflammation and in this paper, we revealed that both are correlated well with the Echo score and decrease in mean gradient after PMBV. CANLPH is a new biomarker and can be used as an SII equivalent in determining the host's inflammation status and can determine the success of the procedure used in MS.

**Ethics Committee Approval:** Ethics committee approval was obtained from Adana City Training and Research Hospital Clinical Research Ethics Committee (02.06.2021, approval number 1432).

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