Turk Kardiyol Dern Ars 2021;49(7):522-532 doi: 10.5543/tkda.2021.39232

ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

The relationship between plasma proadrenomedullin level and severity of the disease in patients with isolated rheumatic mitral stenosis

İzole romatizmal mitral stenozu olan hastalarda plazma proadrenomedullin seviyesi ile hastalık ciddiyeti arasındaki ilişki

Ali Rıza Demir, M.D.[1], İlyas Çetin, M.D.[2], Ali Kemal Kalkan, M.D.[1], Yalçın Avcı, M.D.[1], Mehmet Altunova, M.D.[3], Begüm Uygur, M.D.[1], Emre Yılmaz, M.D.[4], Mehmet Ertürk, M.D.[1]

[1]Department of Cardiology, University of Health Science, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
[2]Department of Cardiology, Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey
[3]Department of Cardiology, İdil State Hospital, Şırnak, Turkey
[4]Department of Cardiology, Görele State Hospital, Giresun, Turkey

ABSTRACT

Objective: In this study, we aimed to determine the plasma proadrenomedullin (ProADM) levels in patients with rheumatic mitral stenosis (MS), to evaluate the relationship between ProADM levels and the echocardiographic parameters that represent the severity of stenosis and symptoms, and to compare the ProADM and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, which is a well-known marker for rheumatic MS.

Methods: Our study included 53 consecutive patients with isolated rheumatic MS and 45 volunteers with similar age and gender features. Patients with MS were divided into two groups based on the presence of an indication for intervention. Detailed echocardiographic examinations were performed on all participants, and blood samples were collected to detect the NT-proBNP and ProADM levels.

Results: NT-proBNP and ProADM levels were significantly higher in the rheumatic MS group compared with the control group. In rheumatic MS groups, patients with an indication for intervention had higher levels of NT-proBNP and ProADM compared with patients without an indication for intervention. Moreover, NT-proBNP and ProADM levels were found to be significantly correlated with echocardiographic parameters, which revealed the severity of stenosis in various degrees. Both parameters increased as the New York Heart Association (NYHA) class increased, and this increase had a statistical significance. Additionally, the cut-off values of both parameters (NT-proBNP: 119.9 pg/mL, ProADM: 6.15 nmol/L) could detect patients with an indication for intervention with high sensitivity and specificity rates. NT-proBNP was found to be slightly more effective in this regard.

Conclusion: The increased NT-proBNP and ProADM levels in patients with isolated rheumatic MS can help clinicians in distinguishing patients with an indication for intervention by providing additional information to echocardiography.

ÖZET

Amaç: Bu çalışmanın amacı romatizmal mitral stenozu (MS) olan hastalarda plazma proadrenomedullin (ProADM) düzeylerini saptamak, ProADM konsantrasyonu ile stenoz ciddiyetinin göstergesi olan ekokardiyografik parametreler ve semptom düzeyi arasındaki ilişkiyi incelemek ve kendini daha önce bu alanda ispatlamış N-terminal pro-brain natriuretic peptide (NT-proBNP) ile ProADM'yi kıyaslamaktır.

Yöntemler: Çalışmaya izole romatizmal MS tanısı ile takip ve tedavi altında olan ardışık 53 hasta ile bu hastalarla benzer yaş ve cinsiyet özelliklerine sahip 45 gönüllü dahil edildi. MS haslarında kendi içinde girişim endikasyonu olanlar ve olmayanlar olarak iki gruba ayrıldı. Tüm deneklere detaylı ekokardiyografi yapılıp, NT-proBNP ve ProADM düzeylerinin tespit edilebilmesi için kan örneği alındı.

Bulgular: Romatizmal MS'i olan hasta grubunda NT-proBNP ve ProADM seviyesi kontrol grubuna göre anlamı düzeyde daha yüksekti. Benzer şekilde romatizmal MS'i olan hastalar içerisinde girişim endikasyonu olan hastalarda, girişim endikasyonu olmayanlara göre bu iki parametre daha yüksek saptandı ($p<0.001$ ve $p<0.001$). Bunun yanı sıra yapılan korelasyon analizinde romatizmal MS'i olan hastalarda NT-proBNP ve ProADM seviyeleri hastalık ciddiyetinin göstergesi olan ekokardiyografik bulgular ile çeşitli derecelerde anlamlı korelasyona sahip olduğu görüldü. Her iki parametrede New York Heart Association (NYHA) sınıfı arttıkça arttı ve bu artış istatistiki bir anlamlılığa sahipti. Bir diğer bulgumuz ise her iki parametre için hesapladığımız kestirim değerlerinin (NT-proBNP: 119.9 pg/mL, ProADM: 6.15 nmol/L) yüksek duyarlılık ve özgüllük oranlarıyla girişim endikasyonu olan hastaları tespit edebiliyor olmasıydı. NT-proBNP bu anlamda az farkla daha etkili görüldü.

Sonuç: İzole romatizmal MS'i olan hastalarda artmış olan NT-proBNP ve ProADM düzeyleri ekokardiyografiye ek bilgiler sağlayarak girişim endikasyonu olan hastaların ayırt edilebilmesinde klinisyenlere yardımcı olabilir.

Received: November 23, 2020 *Accepted:* February 23, 2021
Correspondence: Ali Rıza Demir, M.D. Department of Cardiology, University of Health Science, İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
Tel: +90 505 749 84 71 e-mail: alirdemir1986@gmail.com

Although the frequency of rheumatic mitral stenosis (MS) has decreased in developed countries, it is still common in developing countries and continues to be a serious health problem.[1,2] The main aim of the intervention in patients with MS is to restore the limitation of the functional capacity. The determination of the procedure time is one of the most important points in this patient group. Clinical symptoms such as dyspnea and fatigue are generally observed when the valve area is <1.5 cm^2 at rest. Two-dimensional and Doppler echocardiographic methods are currently used to determine the severity of MS. However, as these methods require a certain quality of echocardiographic image, difficulties are experienced in patients with insufficient echogenity.

Brain natriuretic peptide (BNP) is a neurohormone that is synthesized and secreted from both ventricular and atrial myocytes in response to increased wall tension. After it is synthesized as a prohormone, it is divided into the active part, BNP, and the inactive part, N-terminal BNP.[3] It has diuretic, natriuretic, and vasodilator effects.[4] It is a sensitive marker for left ventricular dysfunction.[5,6] In addition, previous studies showed that the N-terminal pro-brain natriuretic peptide (NT-proBNP) levels increased in patients with rheumatic MS, and this increase was associated with the severity of stenosis and symptoms.[7-9] However, the role of proadreomedullin (ProADM), which is a more recent biomarker, remains unclear in MS patients. ProADM is a precursor of adrenomedullin (ADM) hormone. ADM, first described in 1993, has a peptide structure that is isolated from human pheochromocytoma tissue and has vasodilator and hypotensive effects. Its plasma concentration does not vary on the basis of age or gender.[10] In an animal study, it has been shown that cardiac mechanical tension increased the mRNA levels of ADM.[11]

In this study, we aimed to detect the plasma ProADM levels in patients with rheumatic MS, to evaluate the relationship between ProADM levels and echocardiographic parameters that revealed the severity of stenosis and symptoms, and to compare ProADM and NT-proBNP, which is a well-known marker for rheumatic MS.

METHODS

Study population

In our study, we included 53 consecutive patients with isolated rheumatic MS who underwent echocardiographic examination between September 2017 and March 2018, and 45 volunteers with similar age and gender features. The study was approved by the ethics committee (date: November 21, 2017; decision no: 2017/22) of Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital. This study was conducted in accordance with the requirements of the Declaration of Helsinki. Verbal and written informed consents were obtained from each study participant.

Abbreviations:

ADM	*Adrenomedullin*
AUC	*Area under curves*
BNP	*Brain natriuretic peptide*
CI	*Confidence interval*
CV	*Coefficient of variation*
GFR	*Glomerular filtration rate*
HDL-C	*High-density lipoprotein cholesterol*
LA	*Left atrium*
LDL-C	*Low-density lipoprotein cholesterol*
LV	*Left ventricle*
LVEDD	*Left ventricular end diastolic diameter*
LVEF	*Left ventricular ejection fraction*
LVESD	*Left ventricular end systolic diameter*
MMG	*Mean mitral gradient*
MS	*Mitral stenosis*
MVA	*Mitral valve area*
NPV	*Negative predictive value*
NT-proBNP	*N-terminal pro-brain natriuretic peptide*
NYHA	*New York Heart Association*
OR	*Odds ratio*
PMG	*Peak mitral gradient*
PPV	*Positive predictive value*
ProADM	*Proadrenomedullin*
ROC	*Receiver operator characteristic*
SD S	*tandard deviation*
sPAP	*Systolic pulmonary artery pressure*
TTE	*Transthoracic echocardiography*

Exclusion criteria were the presence of moderate and severe mitral, tricuspid, and/or aortic regurgitation, aortic stenosis, left ventricular dysfunction on transthoracic echocardiography (TTE), atrial fibrillation, history of cardiac surgery or balloon valvuloplasty, renal or hepatic failure, and coronary or pulmonary disease.

All patients underwent routine evaluation, including medical history, physical examination, 12-lead electrocardiography, two-dimensional echocardiography, and blood tests. Functional capacity was assessed on the basis of the New York Heart Association (NYHA) classification.

Echocardiographic measurement

Transthoracic echocardiographic examination was performed according to the recommendations of the European Association of Cardiovascular Imaging by using a Vivid S5 3S-RS probe (General Electric Viv-

id S5; GE Vingmend Ultrasound AS, Horten, Norway) with a 1.7/3.4 MHz phased-array transducer.[12]

M-mode, two-dimensional, and Doppler echocardiograms were obtained in all subjects in the left lateral decubitus position. Left ventricular (LV) and left atrial (LA) dimensions were measured in the parasternal long-axis view. Rheumatic valvular disease was diagnosed based on features such as thickening of the valve leaflets and chordal apparatus, restricted leaflet separation, diastolic doming of the anterior mitral leaflet, commissural fusion or M-mode detection of diminished mitral E–F slope, and upward movement of posterior mitral leaflet in early diastole. The severity of the stenosis was quantified by planimetry in two-dimensional images, by Doppler measurement of transvalvular gradients and by the estimation of the mitral valve area (MVA) with the pressure half-time method. In addition, peak mitral gradient (PMG) and mean mitral gradient (MMG) were obtained. The maximal velocity of the tricuspid regurgitant jet was assessed by continuous wave Doppler echocardiography from a low parasternal, long-axis view of the right ventricular inflow or apical and subcostal views. The pressure gradient between the right ventricle and right atrium was calculated by applying the Bernoulli equation. An estimated right atrial pressure by using phasic respiratory inferior vena cava dimensions was added to the transtricuspid gradient in order to calculate the peak systolic pulmonary artery pressure (sPAP).

The intra- and inter-observer differences for echocardiographic data were less than 5%.

Laboratory measurements

Venous blood samples were drawn from all patients within 30 min after the echocardiographic examination from an antecubital vein into the ethylenediamine tetra-acetic acid (EDTA) Vacutainer test tubes (Mediost BV, Doesburg, the Netherlands) after 30 min of supine rest. The samples were immediately placed on ice, and plasma separation was performed at 4°C.

For NT-proBNP determination, an electrochemiluminescence immunoassay (ProBNP Elecsys system, Roche Diagnostics GmbH, Mannheim, Germany) was used. For the evaluation of the renal function, serum creatinine levels were determined and glomerular filtration rate (GFR) was calculated using the 2009 CKD-EPI creatinine equation.[13]

ProADM levels were measured using a commercial human ProADM radioimmunoassay kit (Cusabio Biotech, Wilmington, DE). The intra-assay coefficient of variation (CV) of the kit was <8% and the inter-assay CV was <10%. The standards or samples were then added to the appropriate microtiter plate wells with a biotin-conjugated antibody preparation specific for ProADM, and Avidin (Innova Biosciences, Cambridge, UK) conjugated to horseradish peroxidase was added to each microplate well and was incubated. This was followed by the addition of a 3,3′,5,5′ tetramethyl-benzidine substrate solution to each well. Only the wells that contained ProADM, biotin-conjugated antibody, and enzyme-conjugated Avidin exhibited a change in color. The enzyme-substrate reaction was terminated by the addition of sulfuric acid solution, and the color change was measured spectrophotometrically at a wavelength of 450 nm±2 nm. The values of ProADM were provided as nmol/L.

Indications for intervention

Intervention indications for patients with rheumatic MS were defined according to the latest European Society of Cardiology valvular heart disease guidelines as follows:[14]

Symptomatic patients with MVA ≤1.5 cm^2.

Asymptomatic patients with MVA ≤1.5 cm^2 and high thromboembolic risk features such as systemic emboli, dense spontaneous echo contrast in left atrium, and newly developed atrial fibrillation.

Asymptomatic patients with MVA ≤1.5 cm^2 and high hemodynamic decompensation risk features such as systolic pulmonary pressure >50 mmHg at rest, scheduled major non-cardiac surgery, and pregnancy.

Patients with MVA ≤1.5 cm^2 and symptomatic with exercise test.

Statistical analysis

The data was analyzed using the Statistical Package for the Social Sciences, version 24.0 (IBM SPSS Corp., Armonk, NY, USA). Whether the variables showed normal distribution, visual (histograms and probability curves) and analytical methods (Kolmogorov-Simirnov or Shapiro-Wilk) were evaluated. The numerical variables showing normal distribution were expressed as mean±standard deviation (SD), numerical variables not showing normal distribution were expressed as median (interquartile range), and categorical variables as

Table 1. Comparison of the mitral stenosis group and control group according to the basal demographics and laboratory results

Variables	Control (n=45)	Mitral Stenosis (n=53)	*p*
Age (years)	39.0±10.5	41.4±9.6	0.246
Male, n (%)	10 (22.2)	7 (13.2)	0.240
Body mass index, kg/m^2	27.53±5.21	27.95±4.82	0.684
Diabetes mellitus, n (%)	5 (11.1)	10 (18.9)	0.288
Hypertension, n (%)	7 (15.6)	8 (15.1)	0.950
Smoker, n (%)	14 (31.1)	9 (17.0)	0.100
Systolic blood pressure (mmHg)	122.0±10.0	125.2±5.6	0.049
Diastolic blood pressure (mmHg)	73.0±7.3	75.0±4.4	0.095
Heart rate (bpm)	75 (70-79)	78 (71-85)	0.716
LDL-C (mg/dL)	95 (82-123)	102 (81-123)	0.747
HDL-C (mg/dL)	50 (41-61)	46 (39-62)	0.505
Total cholesterol (mg/dL)	179 (158-207)	174 (148-201)	0.543
Triglyceride (mg/dL)	126 (76-174)	103 (75-161)	0.451
Glucose (mg/dL)	91 (84-96)	91 (86-98)	0.491
Hemoglobin (g/dL)	13.63±1.65	12.62±1.34	0.001
White blood cells (10^3/uL)	8.44±2.25	8.08±2.34	0.449
Platelet (10^3/uL)	295±62	273±53	0.069
Neutrophil (10^3/uL)	4.67 (3.80-5.56)	5.19 (3.50-6.12)	0.597
Lymphocyte (10^3/uL)	2.52 (2.16-2.76)	1.99 (1.62-2.75)	0.237
C- reactive protein (mg/dL)	1.7 (1.0-3.9)	2.2 (1.4-5.2)	0.087
Creatinine (mg/dL)	0.65 (0.56-0.78)	0.65 (0.60-0.78)	0.552
Glomerular filtration rate (mL/min)	113±13	106±18	0.029
NT-proBNP (pg/mL)	34.2 (18.3-54.5)	191.0 (89.7-439.0)	<0.001
ProADM (nmol/L)	4.13 (2.08-5.89)	7.84 (5.14-9.89)	<0.001

Data are presented as percentage, mean±standard deviation or median (interquartile range).
LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; NT-proBNP: N-terminal pro-brain natriuretic peptide; ProADM: proadrenomedullin.

percentage (%). The numerical variables such as plasma NT-proBNP and ProADM levels were evaluated using Student t tests and the Mann-Whitney U test between the two groups. Chi-Square or Fisher exact test was used to compare the categorical variables. If there were more than two groups, numerical variables were evaluated using the Kruskal-Wallis test. Multivariable logistic regression analysis was performed to determine the independent predictors associated with the indication for intervention and high ProADM levels. The correlation between plasma NT-proBNP and ProADM levels and the other numerical variables were identified using Pearson or Spearman tests, and a receiver operator characteristic (ROC) curve analysis was carried out to determine the NT-proBNP and ProADM cut-off values for the diagnosis of rheumatic MS in patients with an intervention indication. The area under the ROC curve (AUC) of >0.5, $p < 0.05$ was accepted as statistically significant.

When the alpha error was accepted as 0.01, the power of the study was determined as 0.99 with the G-Power 3.1.9.2 program by using the current sample size and ProADM levels.

RESULTS

In our study, we included 53 patients with isolated rheumatic MS and 45 volunteers with similar age and gender features. The comparison of the MS group and control group in terms of demographics and laboratory results is presented in Table 1. Plasma NT-proBNP

Table 2. Comparison of the mitral stenosis group and control group in terms of echocardiographic parameters

Variables	Control (n=45)	Mitral Stenosis (n=53)	*p*
LVEF (%)	65.6±2.6	62.4±3.1	<0.001
LVEDD (mm)	46.0±3.0	46.3±3.7	0.666
LVESD (mm)	29.7±3.0	28.5±4.0	0.111
Left atrial diameter (mm)	33.5±4.6	43.2±6.2	<0.001
Mitral valve area (cm^2)	4.92±0.76	1.37±0.59	<0.001
Mean mitral gradient (mmHg)	2.0 (1.0–2.0)	9.0 (5.0-13.0)	<0.001
Peak mitral gradient (mmHg)	3.9±1.3	17.7±7.9	<0.001
sPAP (mmHg)	18.0 (17.0-20.5)	45.0 (29.0-59.5)	<0.001
Mild mitral regurgitation, n (%)	10 (22.2)	26 (49.1)	0.006
Mild aortic regurgitation, n (%)	6 (13.3)	15 (28.3)	0.072
Mild tricuspid regurgitation, n (%)	12 (26.7)	24 (45.3)	0.057

Data are presented as mean±standard deviation or median (interquartile range).
LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; sPAP: systolic pulmonary artery pressure.

and ProADM levels were significantly higher in the MS group (p<0.001 and p<0.001, respectively). Additionally, compared with the control group, in the MS group, systolic blood pressure was found to be higher (p=0.001), hemoglobin level (p=0.001) and GFR (p=0.029) were found to be lower. There was no statistically significant difference between groups in terms of other parameters.

In Table 2, groups are compared in terms of echocardiographic parameters. There was no significant difference between the groups in terms of left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), and mild tricuspid and aortic regurgitation rate. However, in the MS group, left ventricular ejection fraction (LVEF) and MVA were lower and LA diameter, PMG, MMG, sPAP, and mild mitral regurgitation rate were higher.

The correlation of the plasma NT-proBNP and ProADM levels with other numerical variables is shown in Table 3. NT-proBNP levels had a weak positive correlation with age, weak negative correlation with GFR, moderate positive correlation with LA diameter, sPAP, PMG, MMG and Wilkins score, and a moderate negative correlation with MVA. ProADM levels had a moderate positive correlation with LA diameter, sPAP, PMG, MMG and Wilkins score, and a moderate negative correlation with MVA. The NT-proBNP level had higher correlation coefficient than that of the ProADM level for all the variables that reached significance level, except sPAP. In addition, weak positive correlation was found between NT-proBNP and ProADM levels (r=0.448, p<0.001).

Patients with rheumatic MS were divided into two groups on the basis of the presence of indication for intervention. A total of 32 (60.4%) patients had indication for intervention. In our study, patients with moderate and severe mitral regurgitation and other severe valvular pathologies were excluded; therefore, the majority of our patients who had indication for intervention were suitable candidates for percutaneous mitral balloon valvuloplasty. One patient with LA thrombus and two patients with high Wilkins score were referred for mitral valve replacement. When these two groups were compared, the group with intervention indication was older (p=0.010), had higher body mass index (p<0.001) and lower GFR (p=0.037). Plasma NT-proBNP and mid-regional ProADM levels were significantly higher in the group with intervention indications than in the group without intervention indications. As expected, the LA diameter, sPAP, PMG, and MMG were higher, and MVA was lower in the group with intervention indications (Table 4). Multivariate regression analysis was performed with non-echocardiographic parameters, which were significantly different from the binary analysis to determine the independent predictors of the presence of intervention indication (Table 5). As a

Table 3. Correlation of plasma NT-proBNP and ProADM levels with other numerical variables

	NT-proBNP		ProADM	
Variables	r	*p*	r	*p*
Age	0.391	0.005	0.239	0.087
Glomerular filtration rate	-0.323	0.021	-0.219	0.119
LVEF	-0.140	0.328	0.064	0.654
LVEDD	0.002	0.992	0.152	0.282
LVESD	0.080	0.576	0.176	0.212
Left atrial diameter	0.581	<0.001	0.502	<0.001
Mitral valve area	-0.668	<0.001	-0.574	<0.001
Mean mitral gradient	0.575	<0.001	0.533	<0.001
Peak mitral gradient	0.607	<0.001	0.580	<0.001
sPAP	0.554	<0.001	0.653	<0.001
Wilkins score	0.662	<0.001	0.601	<0.001
ProADM	0.448	<0.001		
NT-proBNP			0.448	<0.001

NT-proBNP: N-terminal pro-brain natriuretic peptide; ProADM: proadrenomedullin; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; sPAP: systolic pulmonary artery pressure.

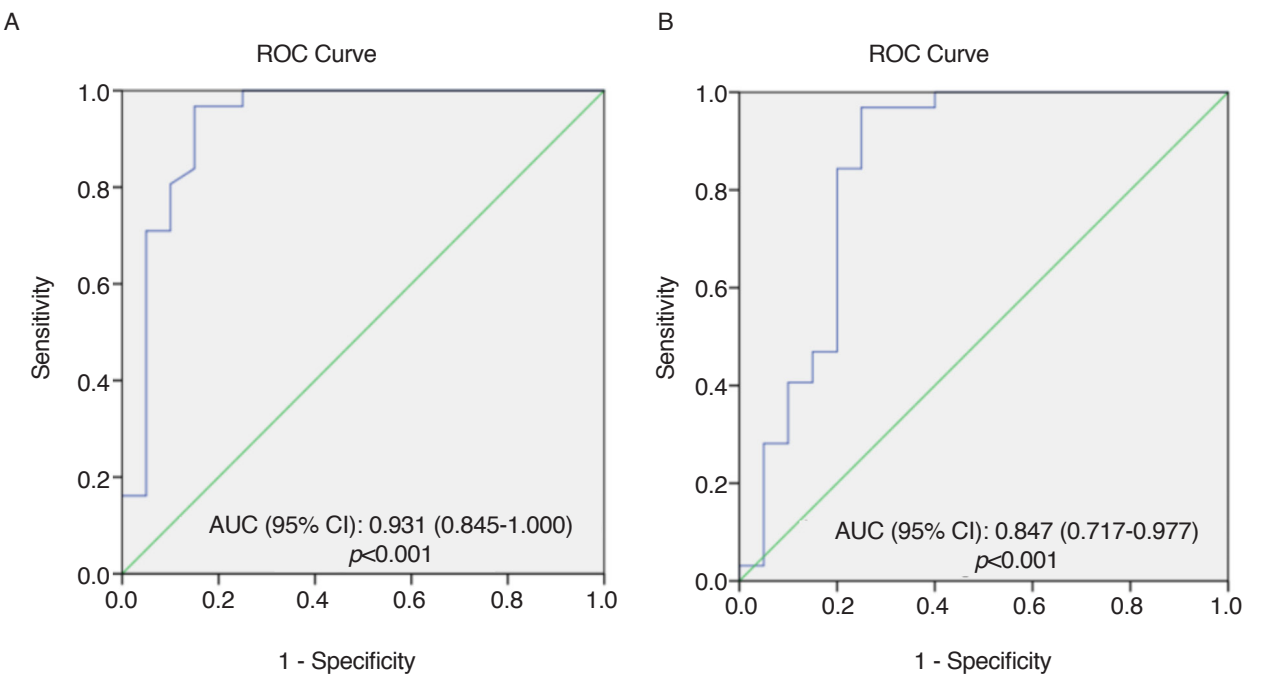

Figure 1. ROC curves for the plasma **(A)** NT-proBNP and **(B)** ProADM levels to detect the patients with intervention indications. ROC: receiver operator characteristic; AUC: area under curves; CI: confidence interval; NT-proBNP: N-terminal pro-brain natriuretic peptide; ProADM: proadrenomedullin.

result of the analysis, both NT-proBNP (p=0.015) and ProADM (p=0.019) were found to be associated with the presence of intervention indication.

Separate ROC curves were performed for the plasma NT-proBNP and ProADM levels to detect the patients with intervention indications (Figure 1). According to

Table 4. Comparison of patients with MS with and without intervention indications in terms of variable parameters

Variables	Indication for intervention (-) (n=21)	Indication for intervention (+) (n=32)	*p*
Age (years)	37.3±6.6	44.1±10.4	0.010
Male, n (%)	3 (14.3)	4 (12.5)	1.0
Body mass index (kg/m^2)	25.18±3.47	29.83±4.74	<0.001
Glomerular filtration rate (mL/min)	112±11	102±20	0.037
NT-proBNP (pg/mL)	79.7 (44.8–107.6)	344.0 (191.0–566.3)	<0.001
ProADM (nmol/L)	4.60 (2.54–6.74)	9.38 (7.36–10.49)	<0.001
LVEF (%)	62.4±2.6	62.4±3.4	0.949
LVEDD (mm)	45.9±3.5	46.6±3.9	0.517
LVESD (mm)	28.1±3.9	28.8±4.2	0.598
Left atrial diameter (mm)	39.1±5.2	45.8±5.2	<0.001
Mitral valve area (cm^2)	1.97±0.45	0.98±0.20	<0.001
Mean mitral gradient (mmHg)	5.0 (4.0-6.0)	12.0 (9.6-15.0)	<0.001
Peak mitral gradient (mmHg)	11.0 (8.5-12.0)	20.0 (18.0-25.8)	<0.001
sPAP (mmHg)	27.0 (21.0-30.0)	55.0 (46.3-63.8)	<0.001
Mild mitral regurgitation, n (%)	9 (42.9)	17 (53.1)	0.465
Mild aortic regurgitation, n (%)	5 (23.8)	10 (31.3)	0.556
Mild tricuspid regurgitation, n (%)	10 (47.6)	14 (43.8)	0.782
Wilkins score	4 (4-5)	7 (6-8)	<0.001

Data are presented as percentage, mean±standard deviation or median (interquartile range).
NT-proBNP: N-terminal pro-brain natriuretic peptide; ProADM: proadrenomedullin; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; sPAP: systolic pulmonary artery pressure.

Table 5. Multivariable logistic regression analysis for the presence of indication for intervention

	Multivariable analysis		
Variables	OR	95% CI	*p*
Age	0.963	0.811-1.142	0.663
Body mass index	1.283	0.995-1.655	0.055
Glomerular filtration rate	0.981	0.898-1.072	0.678
NT-proBNP	1.009	1.002-1.016	0.015
ProADM	1.828	1.106-3.021	0.019

OR: odds ratio; CI: confidence interval; NT-proBNP: N-terminal pro-brain natriuretic peptide; ProADM: proadrenomedullin.

the ROC curves, the best cut-off value for NT-proBNP was 19.9 pg/mL [p<0.001, AUC (95% CI)=0.931 (0.845–1.000)] and for ProADM was 6.15 nmol/L [p<0.001, AUC (95% CI)=0.847 (0.717-0.977)] to determine the patients with intervention indications. AUC for NT-proBNP was higher than that of ProADM. The power of both parameters' cut-off values such as sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in detecting the patients with intervention indications is shown in Table 6. In addition, multivariate regression analysis was performed to determine the factors associated with high ProADM levels above the cut-off value (Table 7). In this analysis, only MVA was included among the echocardiographic parameters in order to prevent interaction with each other, and it was found that among all the variables included in the analysis, only MVA was independently associated with high ProADM levels (p=0.001).

Patients with rheumatic MS were classified according to their symptoms. 21 (39.6%) of the patients had NYHA class I symptoms, 17 (32.1%) of the patients had NYHA class II symptoms, 15 (28.3%) of the patients had NYHA class III symptoms. According to the NYHA classes, patients' plasma NT-proBNP and ProADM levels were compared. Both parameters increased with the increase in NYHA class, and this increase was statistically significant (Figure 2).

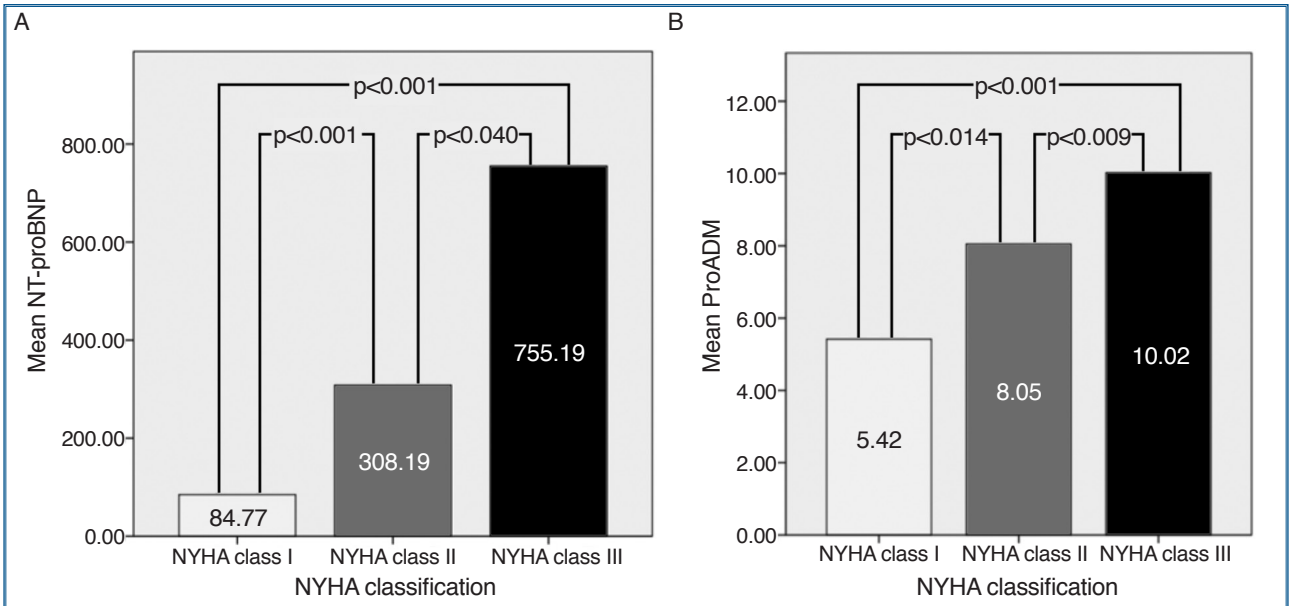

Figure 2. Comparison of plasma **(A)** NT-proBNP and **(B)** ProADM levels according to the NYHA classification.
NT-proBNP: N-terminal pro-brain natriuretic peptide; ProADM: proadrenomedullin; NYHA: New York Heart Association.

Table 6. The power of NT-proBNP and ProADM cut-off values to detect the patients with intervention indications

Variables	Sensitivity	Specificity	PPV	NPV	Accuracy
NT-proBNP >119.9	96.8%	85.0%	90.9%	94.4%	92.2%
ProADM >6.15	96.9%	75.0%	86.1%	93.8%	88.5%

PPV: positive predictive value; NPV: negative predictive value; NT-proBNP: N-terminal pro-brain natriuretic peptide; ProADM: proadrenomedullin.

Table 7. Multivariable logistic regression analysis for high ProADM level

	Multivariable analysis		
	OR	95% CI	*p*
Age	0.981	0.872-1.104	0.749
Male	0.795	0.096-6.564	0.831
Body mass index	0.992	0.846-1.163	0.917
Glomerular filtration rate	0.990	0.925-1.060	0.780
Mitral valve area	0.074	0.015-0.354	0.001

OR: odds ratio; CI: confidence interval; ProADM: proadrenomedullin.

DISCUSSION

In our study, we found that NT-proBNP and ProADM levels were significantly higher in the rheumatic MS group compared with the control group. In the rheumatic MS group, patients with intervention indications had higher levels than those in patients without intervention indications. Moreover, we showed that in patients with rheumatic MS, NT-proBNP and ProADM levels were correlated with echocardiographic parameters and symptoms. The other finding was that the cut-off values of both parameters had high sensitivity and specificity to detect the patients with intervention indications.

Natriuretic peptides are usually synthesized and secreted in ventricular myocytes in response to an increase in LV wall tension and in atrial myocytes because of an increase in atrial wall stress.[15] Their role in determining the diagnosis and prognosis of heart failure is well defined.[16] The previous studies showed that BNP levels increased in rheumatic valve diseases.[9,17] It has been shown that BNP and NT-proBNP levels are associated with an increase in LA wall tension and pulmonary hypertension rather than an increase in LV wall stress in patients with isolated MS.[7,18] While previous studies commonly focused on natriuretic peptides over the past decade, there is a growing interest in the role of other circu-

lating biomarkers such as ProADM, a stable peptide of the ADM precursor. This peptide is responsible for volume regulation and electrolyte homeostasis.[19] In our study, it has been shown that the narrowing in MVA was independently associated with high ProADM level. This suggests that the increase in atrial wall stress is effective in ProADM synthesis as well as in natriuretic peptides.

Preproadrenomedullin is a precursor peptide of adrenomedullin consisting of 185 amino acids. As a result of the separation of amino acids from the structure of this precursor peptide, first ProADM and then immature adrenomedullin are formed. At the end of the enzymatic destruction, matured adrenomedullin is formed.[20] As the half-life of ADM in the circulation is short, its binding rate to plasma proteins is high, and 85% is found as inactive precursors; hence, a more stable and easy-to-measure precursor ProADM is used in clinical studies.[21] In our study, we preferred ProADM instead of ADM.

Increased ProADM levels are related to the increased mortality and morbidity in patients with heart failure, independent from the natriuretic peptides. ProADM surpasses all other determinants in identifying patients with the highest risk of mortality, particularly within 30 days. A prognostic advantage has been consistently demonstrated for a variety of cardiovascular disease states, including acute heart failure.[19]

In a multinational Biomarkers in Acute Heart Failure (BACH) study on patients with heart failure who were admitted to the emergency department with acute dyspnea, ProADM levels had high prognostic values and compared with the other natriuretic peptides, the prognostic value of ProADM was found to be better.[22] Similarly, in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, 560 patients who were admitted to the emergency department with shortness of breath were evaluated and 180 of them had acute decompensated heart failure. The heart failure group had significantly higher NT-proBNP ($p<0.001$), atrial natriuretic peptide ($p<0.001$), and ProADM ($p<0.001$) levels, while ProADM had the highest AUC for the 1-year mortality. ProADM was found to be an independent predictor for mortality at 1-year [$p<0.001$, hazard ratio (HR)=2.70] and 4-year ($p=0.03$, HR=1.51) follow-ups.[23] Adlbrecht et al.[24] followed 786 patients with chronic heart failure for 24 months. In this period, 223 patients died. In Cox regression analysis age, LVEF, NYHA class, and ProADM levels were found to be the independent predictors of mortality [$p<0.001$, HR (95% CI)=2.12 (1.56-2.88)]. A similar result was also found by Gegenhuber et al.[25] where 137 patients with acute decompensated heart failure were followed up for 12 months. In this period, 41 patients died. ROC curve analysis, for 1-year mortality prediction, showed AUCs of BNP [AUC (95% CI)=0.716 (0.633-0.790)], pro-atrial natriuretic peptide (ProANP) [AUC (95% CI)=0.725 (0.642-0.798)] and ProADM [AUC (95% CI)=0.708 (0.624-0.782)] were similar.

In our study, there was no significant correlation between ProADM level and LVEF. This may be explained by the exclusion of patients with low LVEF from the study. Herein, we aimed to prevent the ProADM level from being affected by a reason other than MS. Again, contrary to expectations, no significant relationship was seen between age, GFR and ProADM levels. Although the correlation between age and ProADM was close to the limit of significance, it was found to be insignificant. The small sample size and the narrow age range may have caused this result. Patients with renal failure were not included in the study. The lowest GFR included in the study was 74 mL/min. It would be more accurate to evaluate the ProADM-GFR relationship by examining patients with various kidney function tests.

Turker et al.[26] evaluated the relationship between mitral regurgitation (MR) and ProADM levels, and they revealed that high ProADM levels were significantly associated with the severity of MR ($p<0.001$) and NHYA class ($p<0.001$). Additionally, they divided the patients with MR into two groups according to the presence of symptoms and they found significantly higher ProADM levels in symptomatic patients [7.50±7.15 nmol/L versus 3.54±3.51 nmol/L, ($p<0.001$)]. Again, according to the 12-month follow-up results of the same study, plasma ProADM levels were significant in univariate analysis [$p<0.001$, HR (95% CI)=1.168 (1.079-1.264)]; however, in multivariate analysis, ProADM levels were not found to be independent predictors [$p=0.169$, HR (95% CI)=1.062 (0.975-1.157)]. Baldenhofer et al.[27] investigated the plasma ProADM levels in patients with severe aortic stenosis who underwent transcath-

eter aortic valve implantation (TAVI), and they found that plasma ProADM levels were independent predictors of 1-year all-cause mortality [p=0.037, HR (95% CI)=3.34 (1.08–10.35)] and cardiovascular events [p=0.036, HR (95% CI)=2.59 (1.07–6.30)] such as NT-proBNP and ProANP levels. Considering these studies, we excluded patients with valvular pathologies other than MS, which may cause an increase in volume or pressure load in the heart cavities and cause an increase in the plasma ProADM level.

Unlike our study, in two studies, plasma ADM level but not ProADM level was investigated in patients with MS. Nishikimi et al.[28] investigated the relationship between plasma ADM level and PAP in patients with MS, and they found that patients with MS had higher ADM concentrations than age-matched normal controls (3.9±0.3 pmol/L versus 2.5±0.3 pmol/L, p<0.001). ADM venous concentrations were correlated with mean PAP (r=0.65, p<0.001), total pulmonary vascular resistance (r=0.83, p<0.001), and pulmonary vascular resistance (r=0.65, p<0.001). Yamamoto et al.[29] investigated the change in ADM level in 15 patients who underwent percutaneous mitral balloon valvuloplasty. They found that plasma ADM level in the peripheral vein was significantly higher in patients with MS (n=15, 59.8±2.7 pg/mL) compared with healthy subjects (n=15, 27.3±3.2 pg/mL, p<0.001).

In our study, we tried to present how the plasma ProADM levels differ in patients with rheumatic MS compared with the controls and according to the severity of stenosis. To the best of our knowledge, there is no study investigating ProADM levels in this group of patients. In addition, we compared the ProADM and NT-proBNP, which is a well-known marker, in terms of its correlation with echocardiographic parameters that revealed the severity of disease and its power in detecting patients requiring intervention. As a result, we represented that NT-proBNP was a more valuable marker, even with a slight difference, compared with ProADM in our study group.

On the other hand, the levels of these two parameters were evaluated according to the symptom levels of the patients, and it was found that they showed a significant increase as the NYHA class increased. The presence of symptoms is an important indication for intervention according to the current guideline recommendations. In clinical practice, these two biomarkers may be considered in patients who have difficulty in expressing their symptoms or in patients whose symptoms cannot be distinguished from any non-cardiac pathology or MS.

Limitations

This study had some limitations. First of all, this study was conducted in a single center and in a relatively small population. In addition to the small size of the group, patients with rheumatic MS were quite heterogeneous in terms of the MVA. The natriuretic peptides other than NT-proBNP were not evaluated. The prospective follow-up data were not included in the study. Again, it may be a good study to show the change in ProADM levels after interventional treatment of rheumatic MS that wasn't included in the study.

Conclusion

The increased NT-proBNP and ProADM levels in patients with isolated rheumatic MS may provide additional information to echocardiography in the evaluation of mitral valve stenosis. Especially when echocardiography has limited image quality, it can be a pathfinder in detecting the severity of disease. In addition, we think that these two parameters can help clinicians to distinguish patients with isolated rheumatic MS with intervention indications. Prospective studies with larger populations are needed to support our findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital (Approval Date: November 21, 2017; Approval Number: 2017/22).

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - A.R.D.; Design - A.R.D., B.U.; Supervision - E.Y., M.E.; Materials - İ.Ç., A.K.K., Y.A.; Data - Y.A., İ.Ç., M.A.; Analysis - A.R.D., M.A.; Literature Search - A.R.D., E.Y; Writing - A.R.D., B.U.; Critical Revision - A.K.K, M.E.

Funding: No funding was received for this research.

Conflict-of-interest: None.

REFERENCES

1. Yau TM, El-Ghoneimi YA, Armstrong S, Ivanov J, David TE. Mitral valve repair and replacement for rheumatic disease. J Thorac Cardiovasc Surg 2000;119:53-60. [Crossref]

2. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis 2005;5:685-94. [Crossref]
3. Koratala A, Kazory A. Natriuretic Peptides as Biomarkers for Congestive States: The Cardiorenal Divergence. Dis Markers 2017;2017:1454986. [Crossref]
4. Abuzaanona A, Lanfear D. Pharmacogenomics of the Natriuretic Peptide System in Heart Failure. Curr Heart Fail Rep 2017;14(6):536-542. [Crossref]
5. Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, et al. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation 1994;90:195-203. [Crossref]
6. Kargın R, Esen O, Pala S, Akçakoyun M, Emiroğlu Y, Arslan K, et al. The relationship between echocardiographic parameters and brain natriuretic peptide levels in acute and chronic mitral regurgitation. Turk Kardiyol Dern Ars 2011;39(3):191-7. [Crossref]
7. Davutoglu V, Celik A, Aksoy M, Sezen Y, Soydinc S, Gunay N. Plasma NT-proBNP is a potential marker of disease severity and correlates with symptoms in patients with chronic rheumatic valve disease. Eur J Heart Fail 2005;7:532-6. [Crossref]
8. Kılıçkesmez KO, Bulut G, Başkurt M, Coşkun U, Yıldız A, Küçükoğlu S. QT dispersion in patients with rheumatic mitral stenosis and its relation with echocardiographic findings and serum NT-proBNP levels. Turk Kardiyol Dern Ars 2011;39:183-90. [Crossref]
9. Uslu N, Orhan AL, Nurkalem Z, Avcı İ, Özer HO, Sarı İ, et al. The relationship of high plasma levels of atrial and brain natriuretic peptides with disease severity in mitral valve stenosis. Turk Kardiyol Dern Ars 2006;34(8):484-488.
10. Minamino N, Kikumoto K, Isumi Y. Regulation of adrenomedullin expression and release. Microsc Res Tech 2002;57:28-39. [Crossref]
11. Tsuruda T, Kato J, Kitamura K, Imamura T, Koiwaya Y, Kangawa K, et al. Enhanced adrenomedullin production by mechanical stretching in cultured rat cardiomyocytes. Hypertension 2000;35:1210-4. [Crossref]
12. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the Echocardiographic Assessment of Aortic Valve Stenosis: A Focused Update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2017;30(4):372-392. [Crossref]
13. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int 2014;85:49-61. [Crossref]
14. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-2791. [Crossref]
15. Maisel AS, Duran JM, Wettersten N. Natriuretic peptides in heart failure: Atrial and b-type natriuretic peptides. Heart Fail Clin 2018;14(1):13-25. [Crossref]
16. Francis GS, Felker GM, Tang WH. A Test in Context: Critical Evaluation of Natriuretic Peptide Testing in Heart Failure. J Am Coll Cardiol 2016;67(3):330-7. [Crossref]
17. Gölbaşı Z, Uçar O, Yüksel AG, Gülel O, Aydoğdu S, Ulusoy V. Plasma brain natriuretic peptide levels in patients with rheumatic heart disease. Eur J Heart Fail 2004;6:757-60. [Crossref]
18. Kilickesmez KO, Ozkan AA, Abaci O, Camlıca H, Kocas C, Kaya A, et al. Serum N-terminal brain natriuretic peptide indicates exercise induced augmentation of pulmonary artery pressure in patients with mitral stenosis. Echocardiography 2011;28:8-14. [Crossref]
19. Potocki M, Ziller R, Mueller C. Mid-regional pro-adrenomedullin in acute heart failure: a better biomarker or just another biomarker? Curr Heart Fail Rep 2012;9:244-51. [Crossref]
20. Kitamura K, Kangawa K, Eto T. Adrenomedullin and PAMP: discovery, structures, and cardiovascular functions. Microsc Res Tech 2002;57:3-13. [Crossref]
21. von Haehling S, Filippatos GS, Papassotiriou J, Cicoira M, Jankowska EA, Doehner W, et al. Mid-regional pro-adrenomedullin as a novel predictor of mortality in patients with chronic heart failure. Eur J Heart Fail 2010;12:484-91. [Crossref]
22. Maisel A, Mueller C, Nowak R, Peacock WF, Landsberg JW, Ponikowski P, et al. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. J Am Coll Cardiol 2010;55:2062-76. [Crossref]
23. Shah RV, Truong QA, Gaggin HK, Pfannkuche J, Hartmann O, Januzzi JL Jr. Mid-regional pro-atrial natriuretic peptide and pro-adrenomedullin testing for the diagnostic and prognostic evaluation of patients with acute dyspnoea. Eur Heart J 2012;33:2197-205. [Crossref]
24. Adlbrecht C, Hülsmann M, Strunk G, Berger R, Mörtl D, Struck J, et al. Prognostic value of plasma midregional pro-adrenomedullin and C-terminal-pro-endothelin-1 in chronic heart failure outpatients. Eur J Heart Fail 2009;11:361-6. [Crossref]
25. Gegenhuber A, Struck J, Dieplinger B, Poelz W, Pacher R, Morgenthaler NG, et al. Comparative evaluation of B-type natriuretic peptide, mid-regional pro-A-type natriuretic peptide, mid-regional pro-adrenomedullin, and Copeptin to predict 1-year mortality in patients with acute destabilized heart failure. J Card Fail 2007;13:42-9. [Crossref]
26. Turker Y, Aslantas Y, Turker Y, Akkaya M, Ucgun T, Erkan ME. A novel indicator for assessment of mitral regurgitation severity: pro-adrenomedullin. Int J Cardiol 2013;168:2998-3000. [Crossref]
27. Baldenhofer G, Laule M, Mockel M, Sanad W, Knebel F, Dreger H, et al. Mid-regional pro-adrenomedullin (MR-proADM) and mid-regional pro-atrial natriuretic peptide (MR-proANP) in severe aortic valve stenosis: association with outcome after transcatheter aortic valve implantation (TAVI). Clin Chem Lab Med 2017;55:275-283. [Crossref]
28. Nishikimi T, Nagata S, Sasaki T, Tomimoto S, Matsuoka H, Takishita S, et al. Plasma concentrations of adrenomedullin correlate with the extent of pulmonary hypertension in patients with mitral stenosis. Heart 1997;78:390-5. [Crossref]
29. Yamamoto K, Ikeda U, Sekiguchi H, Shimada K. Plasma levels of adrenomedullin in patients with mitral stenosis. Am Heart J 1998;135:542-9. [Crossref]

Keywords: Mitral stenosis; natriuretic peptide; adrenomedullin

Anahtar Kelimeler: Mitral stenoz; natriüretik peptid; adrenomedüllin