# Relationship between Serum Levels of BNP and Left Ventricular Mechanics with Severity of Mitral Regurgitation in Asymptomatic Patients with Organic Mitral Regurgitation and Preserved Left Ventricular Function

## Organik Mitral Yetmezlikli ve Sol Ventrikül Fonksiyonu Korunmuş Asemptomatik Hastalarda BNP Serum Düzeyleri ile Sol Ventrikül Mekaniği ve Mitral Yetersizliği Ciddiyeti Arasındaki İlişki

Fulya AVCI DEMIR[1], Alexandros PAPACHRISTIDIS[2], Refik Emre ALTEKIN[3], Ibrahim DEMIR[3]

[1]Elmali State Hospital, Cardiology Clinic, Antalya, Turkey
[2]King's College Hospital, Department of Cardiology, London, UK
[3]Akdeniz University Faculty of Medicine, Department of Cardiology, Antalya, Turkey

Correspondence Address
Yazışma Adresi

**Fulya AVCI DEMIR**
Elmali State Hospital, Cardiology Clinic, Antalya, Turkey

E-mail: fulyaavcidemir@gmail.com

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Fulya AVCI DEMİR
ORCID ID: 0000-0003-0608-595X
Alexandros PAPACHRISTIDIS
ORCID ID: 0000-0002-7606-118X
Refik Emre ALTEKİN
ORCID ID: 0000-0002-6438-810X
İbrahim DEMİR
ORCID ID: 0000-0002-5092-3167

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## ABSTRACT

**Objective:** In moderate and severe mitral regurgitation (MSMR), left ventricular systolic dysfunction develops in time. We aimed to investigate the effect of mitral regurgitation on left ventricular mechanics as assessed with 2D strain echocardiography. We also sought to explore the correlation between BNP and severity of MR and also between BNP and LV mechanics.

**Material and Methods:** Twenty four asymptomatic patients with organic MSMR were included. Left ventricular global longitudinal strain (LV-GLS), global circumferential strain and global radial strain were calculated and serum BNP was measured. Patients were divided into two groups according to their BNP value [≥140 pg/ml (group 1) and < 140 pg/ml(group 2)].

**Results:** Demographic data were similar in both groups. Group 1 had higher mitral E and A valve velocities (0.915±0.297 vs. 1.2±0.337, p=0.023 and 0.634±0.191 vs. 0.862±0.255, p=0,035 respectively). There was a significant difference in GLS values between group 1 and 2 (-20.159 ± 0.386 vs. -15.35±0.912, p<0.001, respectively). In correlation analysis, a positive correlation was found between GLS and BNP (r=0.814, p<0.001), BNP and regurgitant volume(r=0.681; p<0.001), BNP and ERO (r= 0.644, p=0.001). ROC analysis was performed and -18.07 was determined as the cut-off value for GLS that can help to categorize patients as low and high risk based on BNP values.

**Conclusion:** We found that, in the absence of LV dilatation or reduced LV ejection fraction, GLS is reduced in asymptomatic organic MR and is well correlated with the BNP level. In asymptomatic patients with significant MR,s left ventricular global longitudinal strain and plasma BNP levels may be useful in determining subclinical dysfunction of the left ventricle for detecting high-risk patients who will benefit from early surgery.

**Key Words:** Brain natriuretic peptide, Echocardiography, Global longitudinal strain, Hemodynamic, Mitral regurgitation

## ÖZ

**Amaç:** Orta ve ciddi mitral yetersizliğinde, sol ventrikül sistolik disfonksiyonu zamanla gelişir. Biz bu çalışmada, mitral yetersizliğinin, sol ventrikül mekanik fonksiyonlarına olan etkisini 2D strain ekokardiyografi ile araştırmayı amaçladık. Ayrıca BNP seviyesi ile LV mekaniği ve MY ciddiyeti arasındaki ilişkiyi araştırdık.

**Gereç ve Yöntemler:** Organik orta ciddi mitral yetmezliği olan yirmi dört asemptomatik hasta çalışmaya dahil edildi. Sol ventrikül global longitudinal strain (LV-GLS), global sirkumferensiyal ve global radyal strain hesaplandı ve serum BNP düzeyi ölçüldü. BNP değerlerine göre [≥140 pg / ml(grup 1) ve <140 pg /ml(grup 2)] hastalar iki gruba ayrıldı.

**Bulgular:** Demografik veriler her iki grupta da benzerdi. Mitral kapak E ve A velositeleri Grup 1 de anlamlı olarak daha yüksekti.(sırasıyla, 0,915±0,297 vs 1,2±0,337, p=0,023 ve 0,634±0,191 vs 0,862±0,255, p=0,035). Grup 1 ve 2 arasında GLS değerlerinde anlamlı fark tespit edildi. (sırasıyla

-20,159±0,386 vs -15,35±0,912, p<0,001). Korelasyon analizinde GLS ve BNP(r=0,814, p<0,001), BNP ve regürjitan hacim (r=0,681; p<0,001), BNP ve ERO(r=0.644, p=0.001) arasında pozitif korelasyon bulundu. Yapılan ROC analizinde GLS için -18.07 düşük ve yüksek riskli hastaları BNP değerlerine göre sınıflandırmaya yardımcı olabilecek cut-off değer olarak belirlendi.

**Sonuç:** Asemptomatik organik MY li hastalarda LV dilatasyonu ve LV ejeksiyon fraksiyonunda azalma görülmeden önce GLS değerinde azalmanın tespit edilebileceğini ve bu değerin BNP seviyesi ile iyi korele olduğunu bulduk. Belirgin MY si olan asemptomatik hastalarda plazma BNP seviyesi ve LV GLS değerinin subklinik sol ventrikül disfonksiyonunun saptanmasında ve erken cerrahiden fayda görecek yüksek riskli hastaların tespit edilmesinde kullanılabileceğini düşünmekteyiz.

**Anahtar Sözcükler:** Brain natriüretik peptit, Ekokardiyografi, Global longitudinal strain, Hemodinamik, Mitral yetmezliği

## INTRODUCTION

The most common cause of primary mitral regurgitation (MR) is myxomatous degeneration of the mitral valve (MV). Surgery, either repair or replacement, is the main management in patients with primary MR because medical management alone does not improve the hemodynamic consequences of the regurgitant valve and does not improve outcomes (1,2). Both current European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend surgical intervention in patients with severe primary MR when symptoms, left ventricular (LV) systolic dysfunction, atrial fibrillation, or pulmonary arterial hypertension occur (3,4).

Development of symptoms or reduced ejection fraction (EF) are class I indications for MV surgery but they are both associated with sub-optimal postoperative outcomes (4). This is attributable to the subclinical structural and microscopic damage in the early period before traditional indications for MV surgery are met (5). There is a growing concern that EF does not reflect true LV systolic function and it only reflects ventricular ejection which is a fraction derived from end-diastolic volume (EDV)(6). In moderate to severe and severe mitral regurgitation, left ventricular volume overload occurs before EF drops. The left ventricle dilates and becomes hyperdynamic. MR causes a condition of increased EDV and reduced afterload, so this incorrectly leads to an overestimation of left ventricular systolic function based on LVEF, even if the LV systolic function has already started to decline. Therefore, there is a need for parameters other than LVEF, which may help to detect early LV dysfunction and optimize the time of surgery, which remains a challenging and controversial decision in patients with asymptomatic primary MR (7).

LV global longitudinal strain (GLS) assessed by speckle tracking echocardiography, has been proposed to be more sensitive to early changes in LV contractile function compared to LVEF (8). In patients with significant MR, abnormal baseline GLS is associated with a reduction in postoperative LVEF (9-14).

Brain natriuretic peptide (BNP) is a hormone secreted from myocardial cells as a response to either diastolic stretch due to volume overload, or wall stress due to pressure overload, and is a marker of LV dysfunction (15-17). Therefore, it is expected to be elevated in long-standing mitral regurgitation. In patients with organic MR, BNP is known to be related to LV function, left atrium (LA) size and systolic pulmonary arterial pressure (SPAP) (18,19). A few studies have suggested that BNP level measurement may be useful for risk stratification and predicting outcomes in patients with asymptomatic primary MR (20-23). We aimed to investigate the effect of mitral regurgitation on left ventricular mechanics. We also sought to find out the correlation between BNP and severity of MR and also between BNP and LV mechanics which may be useful in identifying the subclinical systolic dysfunction in high-risk patients with primary MR who will benefit from early surgery.

## METHODS

### Study population

A total of 24 consecutive asymptomatic patients 18 to 65 years old with at least moderate primary MR (defined as an effective regurgitant orifice (ERO) area >20 $mm^2$ and/or a regurgitant volume (RV) >30 ml) were prospectively recruited between August 2012 and August 2013. Exclusion criterias for our study are listed in Table I.

The present study was approved by the ethics committee of Akdeniz University Faculty of Medicine on 09.04.2013 with the letter number B.30.2.AKD.0.20.05.05 / 8 and all patients provided written informed consent.

### Demographic and clinical data

Demographic and clinical data included age, gender, height, weight, smoking, documented diagnosis of hypertension (patients receiving antihypertensive medications or having untreated hypertension (blood pressure >140/90 mm Hg)), hypercholesterolemia (patients on cholesterol-lowering medication or, in the absence of such medication, low-density lipoprotein cholesterol level >160 mg/dl) and diabetes (patients currently receiving oral medication or insulin).

### Echocardiographic measurements

Echocardiography was performed with a Vivid 7 echocardiography machine (GE-Vingmed Ultrasound AS, Horten,

Norway). All echocardiographic and Doppler data were obtained in digital format and stored on a workstation for offline analysis (EchoPAC, GE Vingmed Ultrasound AS, Horten, Norway). All measurements were averaged over three cardiac cycles. Standard two-dimensional echocardiography, M-mode echocardiography, and Doppler methods were obtained from the apical and parasternal windows according to the recommendations of the American Society of Echocardiography and the related parameters were calculated according to the guidelines (24-26). MR was quantified as previously described (27,28). The RV and the ERO area were calculated with pulsed Doppler volumetric quantitation. Mitral E and A-wave velocities were measured with pulsed-wave Doppler and Ea-wave velocity by tissue Doppler imaging in the septal and lateral position of the mitral annulus. The LV filling pressure was estimated using the E/Ea ratio. SPAP was derived from the regurgitant jet of tricuspid regurgitation using a systolic pressure gradient across the tricuspid valve, as calculated by the modified Bernoulli equation plus right atrial pressure (27). To comprehensively assess LV myocardial function, the global longitudinal strain (GLS), global radial strain (GRS) and global circumferential strain (GCS) were quantified using 2DST analysis. From standard two-dimensional B-mode imaging (frame rate 70-90/s), the endocardial borders were traced at the end-systolic frame, and an automated tracking algorithm outlined the myocardium in successive frames throughout the cardiac cycle. The tracking quality was verified for each segment (with subsequent manual adjustment of the region of interest if necessary), and the myocardial motion was analyzed by speckle tracking within the region of interest bound by endocardial and epicardial borders. Inadequate tracked segments were automatically excluded from the analysis. The local longitudinal strain of each segment was calculated. GLS was obtained by averaging all segment strain values from the apical 4, 3 and 2 chamber views (29,30). GRS and GCS values were obtained from parasternal short-axis images.

## Plasma BNP level measurement

Venous blood samples for baseline BNP measurements were drawn before echocardiography, after 20 min. of supine rest.

## Statistical Analysis

To determine the number of patients needed, a power analysis was performed and it was determined that the study could be performed with 24 patients with 95% strength.

Based on median BNP levels, the patients were divided into two groups. The Shapiro-Wilk test was used to determine the normal distribution of continuous variables. Mean values of variables with normal distribution were tested with the t-test and the not normally distributed variables were tested with the non-parametric Mann-Whitney U test. The results were shown as mean ± standard deviation for the parametric variables and median (minimum-maximum) for the non-parametric variables. Correlations between echocardiographic data (GLS, GRS, GCS, EROA, RV, RF) and BNP level were assessed with the Spearman Test. A ROC analysis was performed to determine a GLS value that could categorize patients as low and high risk based on BNP values. A cut-off value was determined. The statistical analysis was performed using the SPSS 12.0 package and the level of significance was accepted as $p < 0.05$.

# RESULTS

Among the 24 patients (age 18-65 years) included in the study, 7 (29.2%) were male and 17 (70.8%) were female. The BNP values of the patients ranged between 5.06 and 742.3 pg/ml and the median BNP value was 140 pg/ml. Patients were divided into two groups as low (<140 pg/ml) and high (> 140 pg/ml) BNP. 12 patients had moderate and

**Table I:** Exclusion Criteria

| |
|---|
| 1. LV end-systolic diameter > 45 mm, LV ejection fraction < 60% |
| 2. Atrial fibrillation |
| 3. Concomitant more than mild valvular stenosis or regurgitation |
| 4. Known coronary or peripheral vascular disease |
| 5. Left bundle branch block / frequent ventricular extrasystoles in 24-hour ECG. |
| 6. Diabetes mellitus |
| 7. Hypertension |
| 8. Chronic renal disease |
| 9. Cirrhosis |
| 10. Hyperthyroidism |
| 11. Chronic obstructive pulmonary disease |

12 patients had severe MR. The baseline characteristics were similar in the two groups (Table II and III).

There was no significant difference between low and high BNP level groups regarding LV dimensions, ejection fraction and wall thickness (Table III). Patients with a high BNP level had significantly higher mitral inflow E and A velocities (Table IV). There was a significant difference in EROA and RV between two groups (p=0.004, p=0.009, respectively). Patients with severe MR had high EROA and RV values. The left ventricular global longitudinal strain was significantly lower in patients with high BNP levels (-20.159±1.338 in the BNP <140 pg/ml group vs. -15.35±3.159 in the BNP >140 pg/ml group, p< 0.0001). There was no significant difference for GRS and GCS between the two groups (Figüre 1, 2, 3, 4, 5, 6).

**Table II:** Demographic data of the BNP <140 pg/ml vs. BNP ≥140 pg/ml groups

| Variables | BNP <140 pg/ml | BNP >140 pg/ml | *p* |
|---|---|---|---|
| **Age, years** | 42.67±12.63 | 48.25±16.728 | 0.366 |
| **Weight, kg** | 67+/- 9.66 | 69.05+/- 6.84 | 0.594 |
| **Height, cm** | 164.83+/-10.00 | 163.58±8.11 | 0.74 |
| **Body mass index, kg/m²** | 24.80±3.492 | 26.133±4.524 | 0.431 |
| **Heart rate, /min** | 73+/-14 | 76+/-14 | 0.831 |

**Table III:** Echocardiographic Data of BNP <140 pg/ml vs. BNP ≥140 pg/ml groups

| Variables | BNP<140 pg/ml Mean±sd | BNP>140 pg/ml Mean±sd | *p* |
|---|---|---|---|
| **LVEDD (mm)** | 50.67±5.245 | 50.42±4.231 | 0.889 |
| **LVESD (mm)** | 31.50±3.943 | 32.08±2.937 | 0.685 |
| **IVSD (mm)** | 9.92±0.996 | 10.08±1.564 | 0.758 |
| **PWD (mm)** | 9.5 (7-10) | 10 (8-12) | 0.449 |
| **LVMI (g/m²)** | 107.92±22.399 | 109.75±28.262 | 0.862 |
| **EF (%) (BP)** | 68 (60-73) | 62.5 (60-73) | 0.229 |
| **FS (%)** | 36.266±3.776 | 35.725±3.681 | 0.725 |

**Table IV:** Doppler and Strain Values of BNP <140 pg/ml vs BNP ≥140 pg/ml groups

| Variables | BNP<140 pg/ml Mean±sd | BNP >140 pg/ml Mean±sd | *p* |
|---|---|---|---|
| **Mit E** | 0.915±0.297 | 1.2±0.337 | 0.023 |
| **Mit A** | 0.634+/-0.191 | 0.862+/-0.255 | 0.035 |
| **IVRT (msn)** | 81.18±25.678 | 67.64±30.797 | 0.174 |
| **MitDT (msn)** | 80.18±18.707 | 71.64±18.689 | 0.309 |
| **Eort (m/sec)** | 0.097±0.023 | 0.103±0.034 | 0.797 |
| **E/Eort** | 9.63 (5.7-21.2) | 12 (7.7-26.2) | 0.084 |
| **MitS' (ort.) (m/sec)** | 0.075 (0.06-0.11) | 0.07 (0.06-0.25) | 0.642 |
| **Systolic PAB** | 27.5 (21-40) | 35 (27-59) | 0.059 |
| **GRS (%)** | 42.708±24.402 | 41.154±14.725 | 0.813 |
| **GCS (%)** | -13.885 (-29.59-70) | -19.968 (-24.31-13.21) | 0.119 |
| **LV-GLS (%)** | -20.159±1.338 | -15.35±3.159 | <0.001 |
| **EROA (cm2)** | 0.325 (0.24-0.76) | 0.625 (0.34-0.91) | 0.004 |
| **RV (ml)** | 55 (35-134) | 93 (49-120) | 0.009 |
| **RF (%)** | 47.00% ±10.608% | 54.75%±9.468% | 0.072 |
| **VC (cm)** | 4 (3-7) | 4.5 (3-7) | 0.196 |

The relationship between the parameters used to determine the severity of left ventricular subclinical dysfunction and MR severity was calculated using the Spearman correlation test.

The results are shown in Table V.

As observed in the chart, a strong correlation was found between BNP and GLS, and a moderate correlation was found between BNP and RV and between BNP and EROA. The correlation curves are shown in Figure 7, 8, 9 and Figure 10.

**Table V:** Evaluation of the relationship between BNP and LV-GLS and their relationship with Mit-E, Mit- A, EROA, and RV.

| | | BNP | LV-GLS | Mit-E | Mit A | EROA | RV |
|---|---|---|---|---|---|---|---|
| **BNP** | **Rho** | - | ,814** | ,526** | 328** | ,644** | ,681** |
| | **P** | - | ,000 | ,008 | 117 | ,001 | ,000 |
| **LV-GLS** | **Rho** | ,814** | - | ,324 | 228 | ,570** | ,500* |
| | **P** | ,000 | - | ,123 | 284 | ,004 | ,013 |

***Correlation is significant at the 0.05 level (2-tailed). ****Correlation is significant at the 0.01 level (2-tailed).

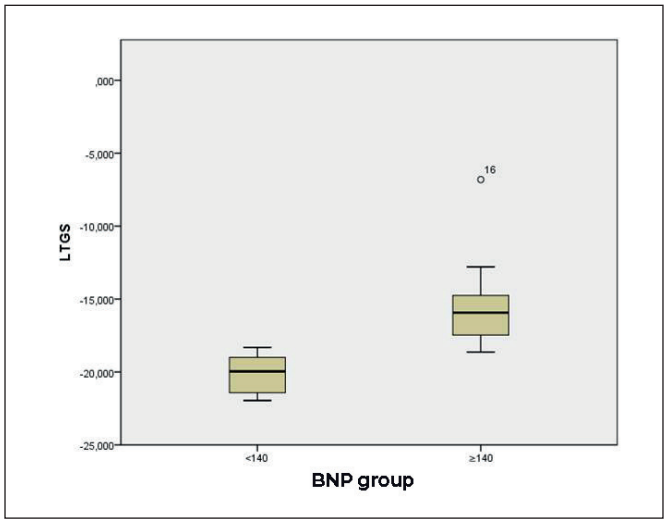


**Figure 1:** Comparison of LV-GLS values between BNP≥140 pg/ml and BNP≥140 pg/ml groups.

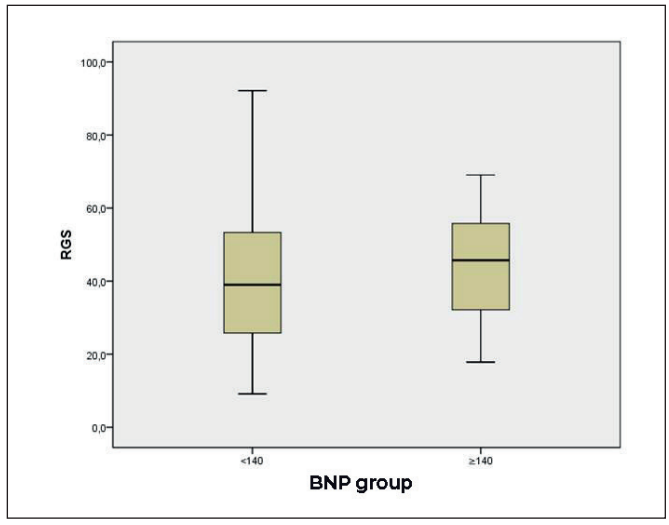


**Figure 2:** Comparison of RGS values between BNP≥140 pg/ml and BNP ≥140 pg/ml groups.

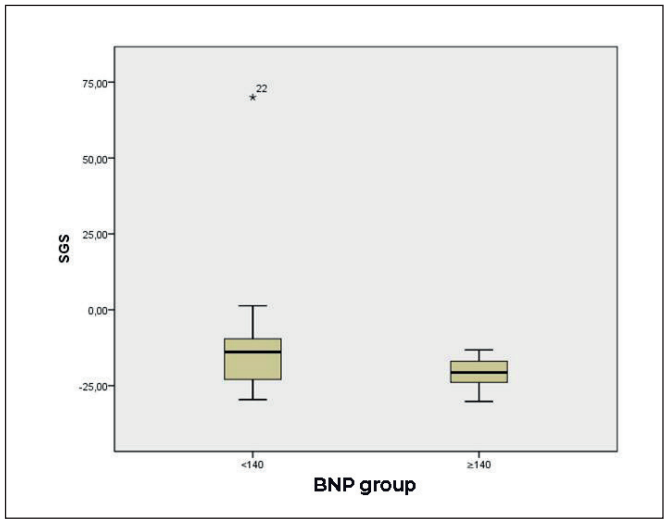


**Figure 3:** Comparison of CGS values between BNP≥140 pg/ml and BNP ≥140 pg/ml groups.

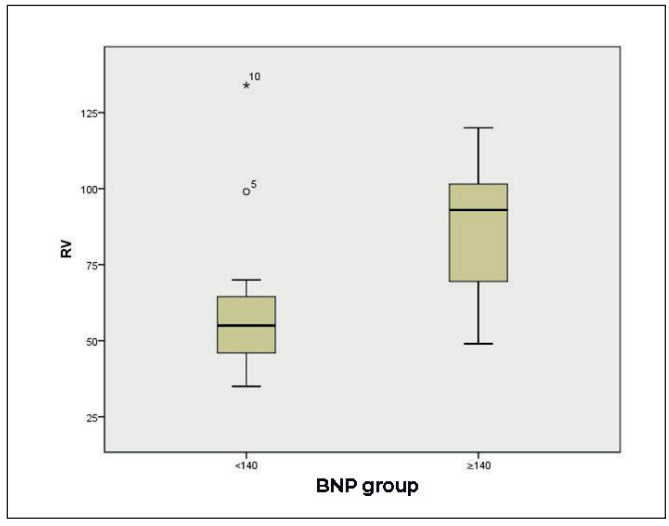


**Figure 4:** Comparison of LRV values between BNP≥140 pg/ml and BNP ≥140 pg/ml groups.

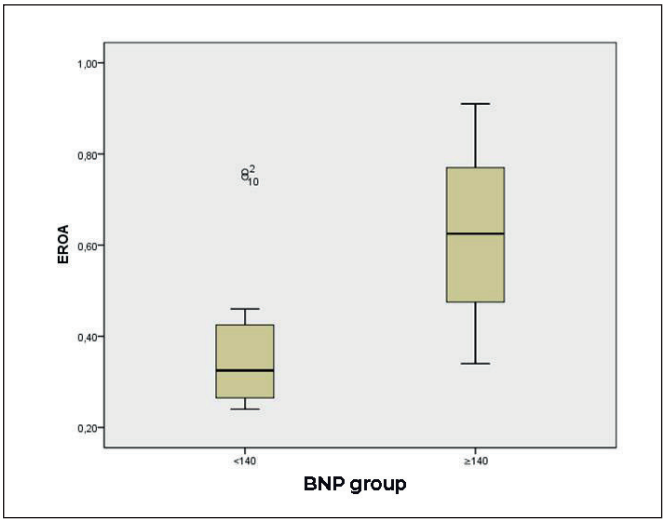


**Figure 5:** Comparison of EROA values between BNP≥140 pg/ml and BNP≥140 pg/ml groups.

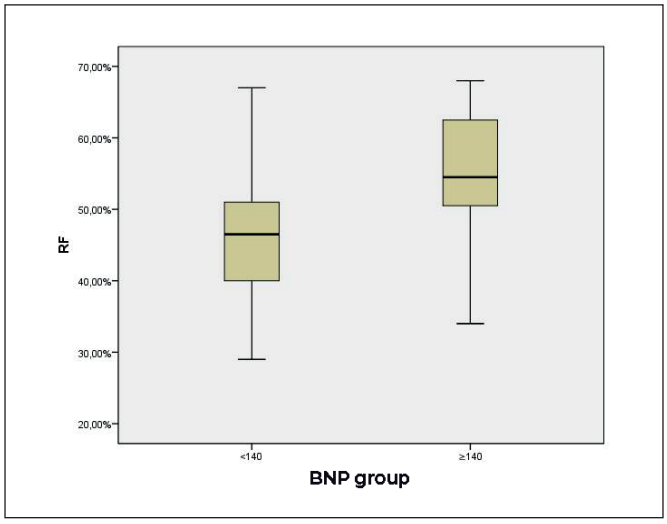


**Figure 6:** Comparison of RF values between BNP≥140 pg/ml and BNP≥140 pg/ml groups.

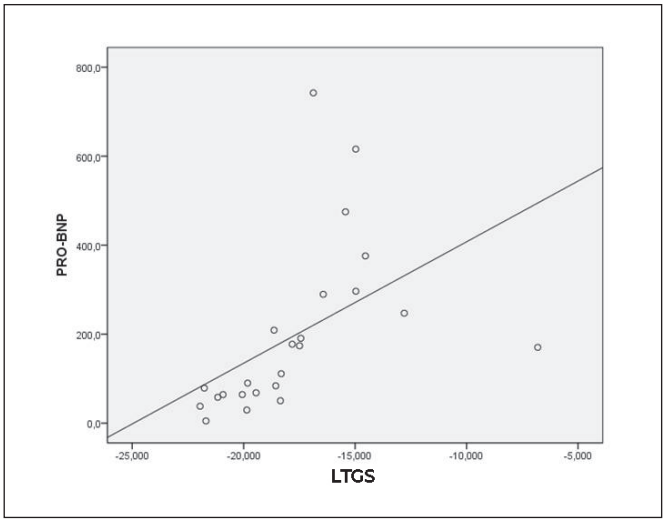


**Figure 7:** Evaluation of the relationship between LV-GLS and BNP.

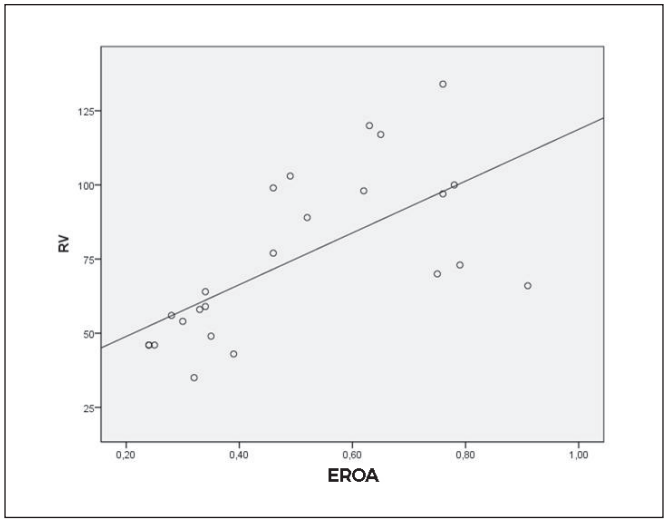


**Figure 8:** Evaluation of the relationship between EROA and RV.

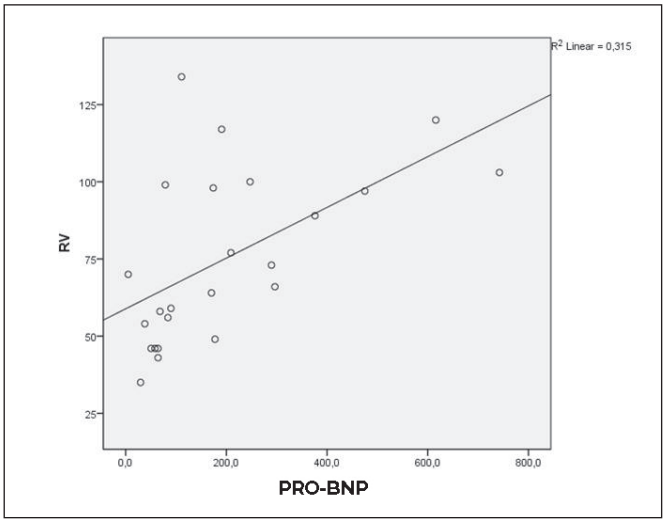


**Figure 9:** Evaluation of the relationship between BNP and RV.

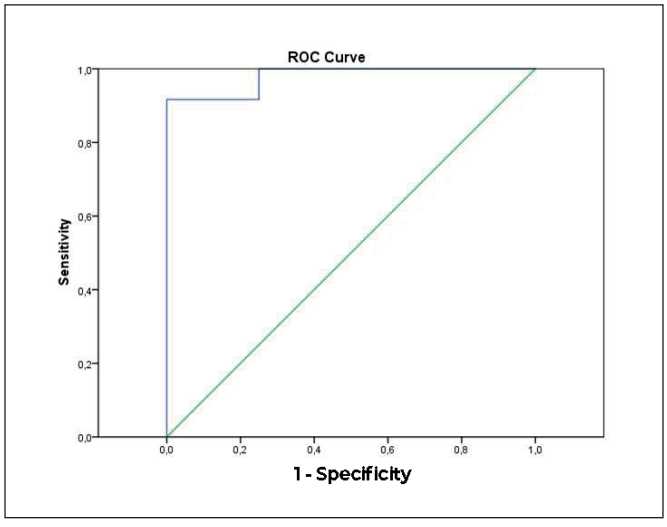


**Figure 10:** ROC curve of LV-GLS.

To test whether GLS is a useful parameter determining the subgroup of high-risk patients (as defined by BNP) who might benefit from early surgery, a ROC analysis was performed. A GLS of -18.07 was obtained as a cut-off value with (AUC) = 0.979 Cut off = -18.07, sensitivity = 0.917, specificity = 1.000, p <0.001.

## DISCUSSION

In our study, we found that the severity of MR as assessed by RV, RF and EROA correlates with the BNP levels. Among the quantitative parameters of MR, the strongest relationship with BNP was observed with RV. The structural changes of the left ventricle as assessed with LV strain analysis correlated well with the BNP levels as well. GLS was the strain parameter that correlated best with the BNP when compared to GRS and GCS.

The brain natriuretic peptide and its inactive amino-terminal fragments are released from the ventricles as a result of volume and/or pressure overload. MR leads to excess volume, LA expansion, and LV remodeling and stimulates BNP activation. The increased wall stress is also responsible for changes in left ventricular architecture which can be detected with echocardiography and in particular with strain and strain rate analysis.

Magne et al. (23) found a median BNP level of 40 pg/ml in a study of 135 asymptomatic patients with moderate to severe MR. Patients were divided into two groups according to this BNP level. Regardless of the severity of MR, age, gender, LV diameter and function, the BNP level was determined as an independent predictor of cardiac events.

Alashi et al. (31) found that BNP and LV-GLS provide synergistic risk stratification, independent of established factors in patients with severe primary MR and preserved LVEF who have undergone mitral valve surgery. In the multivariate linear regression analysis, high BNP levels were independently correlated with the clinical consequences of MR (symptoms, LVESV, LA volume, AF, sPAB). In our study, GLS and RV were found to be correlated to BNP, suggesting that these echocardiographic parameters may be useful in predicting the outcome of patients with moderate or severe primary MR.

In accordance with our findings, Elbey et al. (32), who investigated 31 patients (14 patients with moderate MR, 17 with severe MR), found that plasma BNP levels were significantly higher in patients with severe MR compared to moderate MR and the control group. In another study by Pizarro et al. (20), a cut off value was determined for BNP according to the ROC curve. Major cardiovascular events and death were more frequent in the high BNP group and a high BNP level (BNP > 105 pg/ml) was found to be the strongest independent predictor for LVEDV. Therefore, it may be reasonable to assume that echocardiographic parameters that are well correlated with BNP (i.e. GLS in our study), could be used to predict major cardiovascular events and death, but this needs to be confirmed with an outcome study.

Decreased strain and strain rate values are suggestive of left ventricular dysfunction before changes in LVEF occur. LV strain values can be used to evaluate asymptomatic patients with normal LVEF and moderate to severe organic MR. A GLS of less than -18.07 can predict those patients with increased wall stress (as assessed with BNP) with sensitivity 0.917 and .000. Intervention at this stage to surgically correct MR might be beneficial, but this needs to be explored with large randomized trials.

### Limitations

This is a single-center study with inherent bias and limitations. Despite planning our study based on power analysis, the small number of patients remains a limitation. However, our results are consistent with the literature. We used a vendor-specific software to calculate the LV strain; the cut-off values provided with ROC analysis therefore cannot be applied to strain values calculated with software from other vendors. Although we believe that our findings will be relevant to clinical outcomes, this needs to be investigated with outcome prospective studies, in a larger population.

### Conclusions

Left ventricular subclinical dysfunction is common in patients with MR and normal left ventricular ejection fraction. Our study shows that left ventricular S / SR measurements and plasma BNP levels may be useful in determining subclinical dysfunction of the left ventricle in primary MR patients and can be helpful to detect high-risk patients who will benefit from early surgery.

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