Original Article

# B-type Natriuretic Peptide as an Index of Symptoms and Severity of Chronic Rheumatic Mitral Regurgitation

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## ABSTRACT

**Background:** The most common causes of severe mitral regurgitation (MR) in developing countries are rheumatic heart disease. The plasma level of B-type natriuretic peptide (BNP) is known to increase with left ventricular (LV) dysfunction.

**Aim of the work:** To study BNP level as an index of symptoms and severity of chronic rheumatic MR.

**Patients and Methods:** One hundred and forty patients with rheumatic MR and LV ejection fractions (EFs) of >55% underwent assessment of symptoms, transthoracic echocardiography, and measurement of BNP. Results: The level of BNP rose with increasing left atrium (LA) dimensions and volumes, LV dimensions and volumes, echocardiographic parameters of MR severity (width of the vena contracta, regurgitation jet area, effective regurgitation orifice area, and regurgitant volume), and E waves.

**Results:** BNP was significantly higher in patients with severe MR compared with moderate and mild MR ($P < 0.001$), and using cutoff point of 61 pg/mL mm had 97% sensitivity and 89% specificity for predicting patients with severe MR (0.99, 95% confidence interval [CI] 0.9-1). BNP was significantly higher in patients with New York Heart Association (NYHA III) compared with NYHA II, I and asymptomatic patients ($P < 0.001$) and using cutoff point of 53 pg/mL had 97% sensitivity and 87% specificity for predicting symptomatic patients with symptomatic MR (0.81, 95% CI 0.70-0.92).

**Conclusions:** BNP level increase with increasing severity of rheumatic MR and are higher in symptomatic compared to asymptomatic patients, even in the presence of normal EF%.

**Key words:** B-type natriuretic peptide, mitral regurgitation, rheumatic heart

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## INTRODUCTION

The most common causes of severe mitral regurgitation (MR) in developing countries is rheumatic heart disease.[1] Chronic left ventricular (LV) volume overload as a result of MR leads to compensatory dilatation of the left ventricle. Although this response initially maintains cardiac output, myocardial decompensation eventually results in symptoms of heart failure and an increased risk of sudden death, in addition, backflow into the left atrium (LA) results in enlargement of the LA, atrial fibrillation, and elevated pulmonary pressures.[2]

Echocardiography allows accurate evaluation of the presence or absence, severity, and cause of MR. Although Doppler echocardiography provides several methods of quantifying the severity of regurgitation, none have been shown to predict the clinical outcome.[3]

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The most important aspect of the echocardiographic examination is the quantitation of LV systolic performance. Although calculation of the ejection fraction (EF) is an imperfect means of assessing contractility, from a practical point of view, the EF in conjunction with the end-systolic dimension provides a clinically useful measure of ventricular performance.[4]

In recent years, the measurement of natriuretic peptides in patients with the valvular disease and heart failure has become important.[5,6] The plasma level of B-type natriuretic peptide (BNP) is known to increase with LV dysfunction from many causes, and elevated plasma levels of BNP have been shown to indicate early

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states of myocardial deterioration in various diseases.[7,8] Such findings raised hopes that natriuretic peptides may also be useful in valvular heart disease.[9] Hence, the use of multiple echocardiographic and hormonal parameters in combination can provide an accurate assessment of MR severity and LV dysfunction in most cases.

### Aim of the Work

To study BNP level as an index of symptoms and severity of chronic rheumatic MR.

## PATIENTS AND METHODS

Our study included 140 patients with rheumatic MR, as diagnosed by clinical examination, and conventional echocardiography. They were recruited from the echocardiography unit of the hospital. Patients were classified into three groups; Group I: Forty patients with mild rheumatic MR, Group II: Fifty patients with moderate rheumatic MR, and Group III: Fifty patients with severe rheumatic MR.

### Exclusion Criteria

- Patients with moderate to severe mitral stenosis
- Patients with moderate to severe aortic valve stenosis and regurgitation
- Patients with ischemic heart disease
- Patients with hypertension
- Patients with serum creatinine >2.5 mg/dl.

All patients included in this study were subjected to:

- Detailed history including age, sex, smoking, New York Heart Association (NYHA) functional class
- Complete general and cardiological examinations
- BNP was measured using the RayBio BNP Enzyme Immunoassay (EIA) kit. It is an *in vitro* quantitative assay for detecting BNP peptide based on the principle of competitive EIA. The microplate in the kit was precoated with anti-rabbit secondary antibody. After a blocking step and incubation of the plate with anti-BNP antibody, both biotinylated BNP peptide and peptide standard or targeted peptide in samples interacted competitively with the BNP antibody. Uncompleted (bound) biotinylated BNP peptide then interacted with Streptavidin-horseradish peroxidase (SA-HRP), which catalyzed a color development reaction. The intensity of colorimetric signal was directly proportional to the amount of biotinylated peptide-SA-HRP complex and inversely proportional to the amount of BNP peptide in the standard or samples. This is due to the competitive binding to BNP antibody between biotinylated BNP peptide and peptides in standard or samples. A standard curve of known concentration of BNP peptide was established and the concentration of BNP peptide in the samples was calculated accordingly
- Complete transthoracic echo Doppler study: Echocardiograms were recorded at rest, using ACUSON CV70 echo Doppler machines equipped with a 2.5/3.25-MHz annular array transducer. Patients were studied in left lateral position and electrocardiogram leads were connected to define timing of the cardiac cycle. Parasternal long axis and short axis view and apical 4, 5, and 2 chambers views were obtained the following parameters were studied in each patient:

1. Assessment of the LV: Left ventricular end diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were measured and the LV EF was calculated using, M-mode and biplane modified Simpson's rule. Conventional pulsed wave Doppler echocardiography was used to evaluate trans-mitral LV filling velocities. Peak early diastolic flow velocity (E), peak late diastolic velocities (A), and the ratio of E/A were determined. LV myocardial tissue Doppler velocities were assessed, the sample volume was placed at the lateral and septal margin of the mitral annulus on the apical four chamber view, systolic myocardial velocity (S), early diastolic myocardial velocity (e`), and late diastolic myocardial velocity (a`) were calculated
2. Assessment of the LA: LA size was assessed by M-mode or two-dimensional anteroposterior LA linear dimension which was obtained from the parasternal long axis view. LA volume may also be measured using Simpson's rule
3. Assessment of the severity of MR according to the recommendation of the American society of echocardiography:[10]

a. Vena contracta: The degree of MR was classified according to width of vena contracta into: mild MR if vena contracta <0.3 cm, moderate MR if vena contracta from 0.3 to 0.7 cm, and severe MR if vena contracta >0.7 cm
b. Regurgitation jet area: The degree of MR was classified according to jet area into: mild MR if the jet area <4 $cm^2$, moderate MR if jet area from 4 to 8 $cm^2$, and severe MR if jet area >8 $cm^2$
c. Effective regurgitation orifice area (ERO): Mild MR if the ERO <0.2 $cm^2$, moderate MR if ERO from 0.2 to 0.39 $cm^2$, and severe MR if ERO >0.4 $cm^2$

d. Regurgitation volume (RV): Mild MR if the RV <30 mL/beat, moderate MR if RV from 30 to 59 mL/beat, and severe MR if RV >60 mL/beat

### Statistical Analysis

Statistical package for social sciences (version 15.0, SPSS Inc, Chicago, Ill) was used for data analysis. Data were statistically described in terms of range, mean ± standard deviation (SD), frequencies (number of cases), and relative frequencies (percentages) when appropriate mean and SD were estimates of quantitative data. A $P < 0.05$ is considered statistically significant.

## RESULTS

### Patient Characteristics and Echocardiographic Parameters

Our study included 140 patients with chronic rheumatic MR, 84 female (60%), and 56 male (40%), with mean age 31.8 ± 12.0 years (range, 15–57 years). Weight 62.59 ± 12.4 (range, 35–91 kg), height was 155.13 ± 6.87 (range, 140–167 cm), BSA 1.61 ± 0.16 $m^2$ (range, 1.3–1.92 $m^2$), 131 patients has normal sinus rhythm (94%), nine cases has atrial fibrillation (6%), 21 patients were asymptomatic (15%), 35 patients (25%) had NYHA Class I symptoms, 45 cases (32%) had NYHA Class II symptoms, and 39 cases (28%) had NYHA Class III symptoms, 40 patients (28%) had mild rheumatic MR, 50 patients (36%) had moderate rheumatic MR, and 50 patients (36%) had severe rheumatic MR. There was significant correlation between groups regarding LV dimensions and volumes and contractility, LA dimensions and volumes, degree of MR measured by (vena contracta, regurgitant Jet area regurgitant volumes, and effective orifice area), degree of tricuspid regurgitation, and pulmonary artery systolic pressure. No significant correlation between groups regarding septal wall thickness, posterior wall thickness, RV dimensions, RV functions measured by (fractional area change, tricuspid annular plane systolic excursion method, and S wave velocity of the tricuspid annulus) as shown in Table 1.

### Relation Between Natriuretic Peptides and Echocardiographic Measures

The plasma levels of BNP rose with increasing severity of MR and with increasing LA dimensions and volumes, LV dimensions and volumes, echocardiographic parameters of MR severity (width of the vena contracta, regurgitation jet area, ERO, and regurgitant volume), and E waves. No significant correlation was found

**Table 1: Echocardiographic characteristics of the study groups**

| Variable | Mild MR | Moderate MR | Severe MR | *P* by ANOVA |
|---|---|---|---|---|
| Septal wall thickness (mm) | 7.2±1.88 | 7.9±1.9 | 7.7±1.38 | 0.40 |
| Posterior wall thickness (mm) | 7.3±1.96 | 7.2±1.8 | 7.8±1.4 | 0.35 |
| LVEDD (mm) | 48.65±5.26 | 52.6±4.3 | 59.5±6.7 | <0.0001 |
| LVESD (mm) | 31.08±3.54 | 34.7±4.8 | 39.3±8.9 | 0.0001 |
| EE % M-Mode | 64.82±5.75 | 61.6±8.1 | 58.3±9.44 | 0.015 |
| LVEDV (ml) | 73.04±29.23 | 93.6±22.6 | 125.48±43.5 | <0.0001 |
| LVEDVI (ml/$m^2$) | 44.84±17.5 | 57.0±12.7 | 77.2±27.35 | <0.0001 |
| LVESV (ml) | 31.15±14.16 | 39.6±13.95 | 57.8±24.0 | <0.0001 |
| LVESVI (ml/$m^2$) | 20.4±7.68 | 24.6±7.5 | 36.04±15.9 | <0.0001 |
| SV (ml) | 41.59±15.53 | 53.9±14.0 | 67.3±28.13 | 0.0003 |
| SVI (ml/$m^2$) | 25.88±9.59 | 32.37±8.1 | 42.37±17.6 | 0.0004 |
| EF % by Simpson | 57.69±5.05 | 57.7±6.09 | 53.58±8.8 | 0.063 |
| LA dimension (mm) | 33.43±5.65 | 38.8±6.5 | 51.6±8.12 | <0.0001 |
| LA volume (ml) | 34 0.16±12.95 | 50.3±23.8 | 128.5±58.77 | <0.0001 |
| LAVI (ml/$m^2$) | 20.82±7.23 | 30.45±15.0 | 80.1±38.85 | <0.0001 |
| Vena contracta (mm) | 2.9±0.7 | 4.5±0.69 | 7.5±1.5 | <0.0001 |
| Regurgitant jet area ($cm^2$) | 3.0±0.84 | 5.9±0.87 | 11.4±3.4 | <0.0001 |
| ERO ($cm^2$) | 0.14±0.07 | 0.27±0.08 | 0.55±0.22 | <0.0001 |
| RV (ml/beat) | 22±5 | 45±8 | 71±9 | <0.0001 |
| E wave ( m/s) | 0.86±0.26 | 0.91±0.25 | 1.2±0.4 | <0.001 |
| S mitral annulus | 0.11±0.02 | 0.11±0.03 | 0.13±0.04 | 0.4 |
| e mitral annulus | 0.17±0.04 | 0.12±0.04 | 0.15±0.03 | 0.16 |
| E/e mitral | 5.27±2.11 | 8.5±3.8 | 12.5±5.1 | 0.002 |

LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, EF: Ejection fraction, LVEDV: Left ventricular end diastolic volume, LVEDVI: Left ventricular end diastolic volume index, LVESV: Left ventricular end systolic volume, LVESVI: Left ventricular end systolic volume index, SV: Stroke volume, SVI: Stroke volume index, LA: Left atrium, LAVI: Left atrium volume index, ERO: Effective regurgitant orifice area, RV: Regurgitant volume, E: Wave, early mitral diastolic inflow velocity, S: Systolic mitral annular velocity, e: Mitral annulus, early diastolic mitral annular velocity, E/e: Mitral, ratio of early mitral diastolic inflow velocity and early diastolic mitral annular velocity

**Table 2: Correlation between BNP level and echocardiographic variables**

| Variable | BNP level | |
|---|---|---|
| | *P* | *R* |
| Septal wall thickness (mm) | 0.18 | −0.15 |
| Posterior wall thickness (mm) | 0.85 | −0.22 |
| LVEDD (mm) | <0.001 | 0.48 |
| LVESD (mm) | <0.001 | 0.06 |
| EF % by M-mode | 0.03 | −0.24 |
| LVEDV (ml) | 0.001 | 0.37 |
| LVEDVI (ml/m$^2$) | <0.0001 | 0.44 |
| LVESV (ml) | <0.0001 | 0.4 |
| LVESVI (ml/m$^2$) | <0.0001 | 0.46 |
| SV (ml) | 0.02 | 0.27 |
| SVI (ml/m$^2$) | 0.006 | 0.32 |
| EF % by Simpson | 0.15 | −0.2 |
| LA diameter (mm) | <0.0001 | 0.6 |
| LA volume (ml) | <0.0001 | 0.54 |
| LAVI (ml/m$^2$) | <0.0001 | 0.57 |
| Vena contracta (mm) | <0.001 | 0.48 |
| Regurgitant jet area (cm$^2$) | <0.0001 | 0.57 |
| ERO (cm$^2$) | 0.001 | 0.43 |
| RV (ml/beat) | <0.0001 | 0.43 |
| Mitral E wave (m/s) | 0.001 | 0.39 |
| S mitral annulus | 0.15 | 0.17 |
| e mitral annulus | 0.82 | −0.82 |
| E/e mitral | 0.08 | 0.22 |

LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, EF: Ejection fraction, LVEDV: Left ventricular end diastolic volume, LVEDVI: Left ventricular end diastolic volume index, LVESV: Left ventricular end systolic volume, LVESVI: Left ventricular end systolic volume index, SV: Stroke volume, SVI: Stroke volume index, LA: Left atrium, LAVI: Left atrium volume index, ERO: Effective regurgitant orifice area, RV: Regurgitant volume, E: Wave, early mitral diastolic inflow velocity, S: Systolic mitral annular velocity, e: Mitral annulus, early diastolic mitral annular velocity, E/e: Mitral, ratio of early mitral diastolic inflow velocity and early diastolic mitral annular velocity, BNP: B-type natriuretic peptide

between BNP level and septal wall thickness, and posterior wall thickness [Tables 2 and 3].

## Relation Between Natriuretic Peptides and Severity of Mitral Regurgitation

BNP was significantly higher in patients with severe MR compared with moderate and mild MR ($P < 0.001$) and receiver operating characteristic (ROC) curve analysis showed that BNP 61 pg/mL mm had a 97% sensitivity and 89% specificity for predicting patients with severe MR (0.99, 95% confidence interval [CI] 0.98–1) [Table 4 and Figure 1].

## Relation Between Natriuretic Peptides and Symptoms

BNP was significantly higher in patients with NYHA III compared with NYHA II and I ($P < 0.001$), and ROC curve analysis showed that BNP of 53 pg/mL mm had a 97% sensitivity and 87% specificity for predicting symptomatic patients with MR (0.81, 95% CI 0.70–0.92) [Table 5 and Figure 2].

**Table 3: Correlation between mean values of BNP and echocardiographic parameters**

| Variable | BNP (pg/ml) | *P* |
|---|---|---|
| LA diameter (mm) | | |
| <40 mm (*n*=56) | 31.34±22.82 | <0.001 |
| >40 mm (*n*=84) | 144±108.29 | |
| LAVI (ml/m$^2$) | | |
| <34 (ml/m$^2$) (*n*=68) | 34.5±25.3 | <0.001 |
| <34 (ml/m$^2$) (*n*=72) | 158.8±108.6 | |
| LVEDD (mm) | | |
| <58 mm (*n*=84) | 72.8±89.9 | <0.0013 |
| >58 mm (*n*=56) | 151.5±104.5 | |
| LVESD (mm) | | |
| <40 mm (*n*=96) | 73±88.5 | <0.001 |
| >40 mm (*n*=44) | 163.5±104.8 | |
| LVEDVI (ml/m$^2$) | | |
| <97 ml/m$^2$ (*n*=122) | 99.7±93.8 | <0.004 |
| >97 ml/m$^2$ (*n*=18) | 173.44±129.7 | |
| LVESVI (ml/m$^2$) | | |
| <43 ml/m$^2$ (*n*=122) | 89.2±90.7 | <0.014 |
| >43 ml/m$^2$ (*n*=18) | 178.3±134.5 | |
| EF % | | |
| <55% (*n*=30) | 130.6±96.02 | 0.194 |
| >55% (*n*=110) | 92.17±102.54 | |

LA: Left atrium, LAVI: Left atrium volume index, LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, LVESV: Left ventricular end systolic volume, LVESVI: Left ventricular end systolic volume index, EF: Ejection fraction, BNP: B-type natriuretic peptide

**Table 4: Comparison between mean values of BNP and severity of MR**

| Variable | Mild MR | Moderate MR | Severe MR | *P* |
|---|---|---|---|---|
| BNP (pg/ml) | 18.75±11.2 | 49.7±13.3 | 165±107 | <0.0001 |

BNP: B-type natriuretic peptide, MR: Mitral regurgitation

**Table 5: Correlation between mean values of BNP and severity of symptom**

| Variable | Asymptomatic | NYHA I | NYHA II | NYHA III | *P* |
|---|---|---|---|---|---|
| BNP (pg/ml) | 51.94± 28.73 | 56.34± 28.73 | 139.5± 80.02 | 177.27± 120.06 | <0.0001 |

BNP: B-type natriuretic peptide, NYHA: New York Heart Association

## DISCUSSION

Rheumatic valvular heart disease, particularly MR, accounts for a large proportion of cardiology practice in developing countries. Chronic severe MR leads to volume overload of the LV, which in turn results in compensatory chamber dilation and eccentric hypertrophy. The transition to a decompensated state might be due to a progressive increase in regurgitant volume, a decrease in contractility, an increase in afterload, or a combination of these factors.[11]

A biomarker is defined as a biological molecule that can be identified in a particular disease. A robust biomarker could potentially eliminate the need for some costly imaging studies during routine surveillance and aid in management decisions.[12]

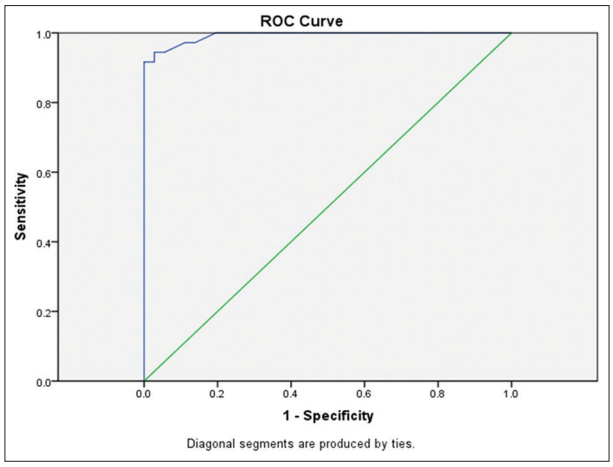


**Figure 1:** Receiver operating characteristic curve for mean values B-type natriuretic peptide and severity of mitral regurgitation

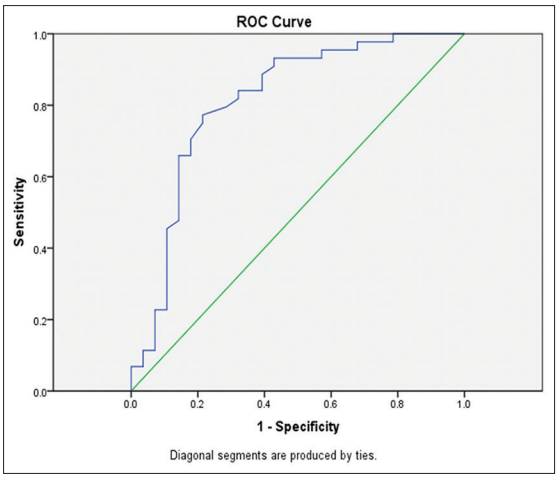


**Figure 2:** Receiver operating characteristic curve for mean values B-type natriuretic peptide and symptomatic mitral regurgitation

BNP are endogenous cardiac hormones secreted by both atrial and ventricular cardiomyocytes in response to end-diastolic wall stress and have been shown clinical utility as biomarkers for diagnosing congestive heart failure, especially when the symptoms and signs are discrete or mild. The cutoff point of BNP recommended for separating the population with heart failure from that without that syndrome is 100 pg/mL.[13] These findings suggest the possibility of expanding the application of BNP measurement to other situations that gradually lead to LV dysfunction, such as rheumatic MR.

Our study evaluated 140 patients with various grades of severity of rheumatic MR. There was a significant correlation between BNP level and the degree of severity of MR ($P < 0.001$). The level of BNP correlated with echocardiographic parameters of MR severity assessed by the width of the vena contracta, regurgitation jet area, ERO, and regurgitant volume ($P < 0.001$).

Our results came in agreement with[14-16] who found a significant positive relationship between BNP level and severity of organic MR. On the other hand, other studies have shown either no correlation or a relationship only on univariate analysis.[17-19]

In our study, BNP was significantly different among different grades of symptoms assessed by NYHA class, and was significantly higher in patients with NYHA Class III compared to patients with Class II, I, and asymptomatic patients ($P < 0.001$), with a mean value of BNP 51.94 ± 28.73 pg/mL in asymptomatic patients, 56.34 ± 76.99 pg/mL in patient with NYHA Class I, 139.5 ± 80.02 pg/mL in patient with NYHA Class II and 177.27 ± 120.06 pg/mL in patients with NYHA Class III.

This was in agreement with Detaint *et al*.[17,18] who demonstrated a significant positive correlation between BNP level and severity of symptoms in patients with organic MR. Other studies have shown a significant correlation between other types of natriuretic peptides and symptoms in a patient with organic MR. Potocki *et al*.[16] and Kerr *et al*.[19] demonstrated a significant correlation between N-terminal pro-BNP and severity of symptoms in a patient with organic MR. Shimamoto *et al*.[20] assessed the correlation between BNP and atrial natriuretic peptide (ANP) levels and symptom in patients with organic MR and found that plasma ANP was increased in patients with NYHA functional Class II symptoms but decreased in those with NYHA Class III and IV symptoms, on the other hand BNP and BNP/ANP ratio were increased progressively for NYHA Class II, III, and IV.

In our study, a cutoff value of BNP 61 pg/mL mm had a 97% sensitivity and 89% specificity for predicting patients with severe MR (0.99, 95% CI 0.98–1) and a cutoff value of BNP 53 pg/mL mm had a 97% sensitivity and 87% specificity for predicting symptomatic patients with symptomatic MR (0.81, 95% CI 0.70–0.92) these data confirm that the values capable for identifying patient with severe MR are much lower than the value used for identifying heart failure and suggest that one should not to wait for value above 100 pg/mL to predict severe symptomatic MR.

Our results came in agreement with Meneghelo *et al*.[21] who used a cutoff value for BNP 15.40 pg/mL and reported 73% sensitivity and 74% specificity for detecting patients with severe MR and a cutoff point 28.40 pg/mL, and reported 87% sensitivity 83% and specificity for detecting patients with symptomatic MR and NYHA Classes II and III. Sutton *et al*.[14] used a cutoff point of BNP > 12 (pmol/L) and reported 75% sensitivity and 85% specificity for identifying symptoms in patient with organic MR.

Furthermore, our study found a good significant correlation between BNP and LA size ($P < 0.0001$) and LA volume index ($P < 0.0001$), week significant correlation between BNP and EF measured by M Mode ($P = 0.03$), and strong significant correlation with LVEDD, LVEDVI, LVESD, and LVSDVI ($P < 0.001$). These results suggest that BNP testing may serve as a marker for LV remodeling in chronic rheumatic MR and may be useful in identifying the earliest stages of LV decompensation. When the echocardiographic assessment is technically difficult, low BNP level would suggest that MR is not severe.

## CONCLUSIONS

In patients with rheumatic MR, plasma levels of BNP rise with increasing severity of MR and are higher in markedly symptomatic than in mildly symptomatic patients, even after adjustment for echocardiographic measures of the severity of regurgitation.

### Recommendations

Separate analysis of BNP level based on the presence of associated comorbidities or other valvular lesions are needed. Larger studies are required for assessment of BNP as a prognostic marker in patients with severe rheumatic MR.

### Limitations of the Study

The cost of BNP affects the number of patients enrolled in the study. Despite these difficulties, the results were significant to draw conclusions.

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