Original Research Article

MEAN LEVELS OF B-TYPE NATRIURETIC PEPTIDE (BNP) IN PATIENTS WITH MITRAL STENOSIS CAUSED BY RHEUMATIC HEART DISEASE

ABSTRACT

OBJECTIVE: Mitral stenosis caused by rheumatic heart disease (RHD) is the most common cause of valvular lesion in adults and prevalent in developing countries like Pakistan. Higher natriuretic peptide (BNP) levels can be observed in patients with moderate to severe untreated mitral stenosis and are associated with higher rates of morbidity and mortality. That is why this study aims to determine the association between levels of pro-BNP with severity (mild. Moderate, and severe) of mitral stenosis.

PATIENTS AND METHODS: This was a clinical prospective study carried out in the department of adult cardiology, national institute of cardiovascular diseases, Karachi from 8th august 2019 to 7th February 2020. Total 68 patients of either gender with age between 25-70 years had mitral stenosis of moderate to severe intensity (mitral valve area ≤1.5 cm^2), diagnosed on echocardiography were included for final analysis. A simple blood sample was taken for the assessment of pro-BNP levels. Questionnaire was used for demographic & clinical data collection and analysed using SPSS version 22.0.

RESULTS: The overall mean age of study subjects was 42.21±11.50 years, ranging from 25 – 70 years. Among them, females were prevalent (n = 43, 63.2%). The overall mean serum BNP level was 1071.12±807.26 pg/ml and the mean difference of serum BNP level was not significant

among groups of gender, age, and diabetes mellitus with p>0.05. Significantly raised levels of BNP were observed in patients with severe mitral stenosis as compared to moderate mitral stenosis, p<0.05

CONCLUSION: In conclusion, the mean BNP levels were higher in patients with severe Mitral Stenosis. Therefore, BNP may be used to complement the clinical and echocardiographic assessments in patients with Mitral Stenosis..

KEYWORDS: B-Type Natriuretic Peptide, Mitral Stenosis, Severity of Mitral Stenosis, valvular heart disease, Pakistan

INTRODUCTION:

Mitral stenosis is the commonest valvular heart disease caused by rheumatic heart disease (RHD) in young adults (1). The prevalence of this disease is declined in developed countries while its still common in developing countries including Pakistan and associated with high rates of morbidity and associated mortality (2, 3). The prevalence of rheumatic heart disease in Pakistan shows a discrepancy depending up on the area of residence. In urban areas the prevalence of RHD reported to be lower than rural areas, 5.7/1000 and 22/1000, respectively (4).

Severity of mitral stenosis can be assessed by various techniques. The severity of MS was based on hemodynamic data and variability in the natural history using the mean gradient, systolic pulmonary artery pressure, and mitral valve area. Echocardiography and Doppler examination are essential for the diagnosis and quantification of the severity of the stenosis. Cardiac hormones such as BNP and ANP also play an important role in determining the severity of valvular heart disease particularly when BNP levels are extremely raised the outcome of patients become poor (5, 6).

B-Type natriuretic peptide (BNP) is a hormone secreted in response to the volume and pressure overload caused by stretching of the cardiac myocytes. Literature from previously data have observed and well documented that extreme rise in pro-BNP levels occurs when there is left ventricular failure or dysfunction. While, on the other hands, some of the previously conducted multiple studies have also shown that plasma BNP levels also rises when there is right ventricular dysfunction or failure such as in pulmonary hypertension, cor pulmonale, pulmonary embolism, and tricuspid regurgitation (7, 8).

The relationship between severity of mitral stenosis (mild, moderate, or severe) is correlated with the levels of BNP but studies in this regard are limited. Iltumur K (9) in his study evaluated patients with mild to severe mitral stenosis and found significantly raised levels of BNP in patients with severe MS as compared to moderate MS while patients with mild MS had normal levels of BNP. In another study, the plasma levels of NT-pro BNP were significantly higher in patients with severe MS than in moderate MS (109.8±5.6 versus 88.3±7.6 pg/ml) (9).

Locally and internationally very few studies have been conducted on cardiac peptide secretion in diseases affecting the right side of the heart. Mitral stenosis affects the right heart along with the left atrium, and increases BNP levels in patients with MS have been demonstrated on several occasions (8). Keeping in view the disease burden of rheumatic mitral stenosis at local level along with scarcity of expertise in echocardiography, we aimed to carry out this study to asses this bio marker in our patient population for which we don't have local data available. As it can potentially help us in assessing disease progression & severity as it is quick to perform, less time consuming & comparatively cheaper.

PATIENTS AND METHODS:

This was a prospective single center clinical study and conducted in the department of Cardiology National Institute of Cardiovascular Diseases (NICVD), Karachi. All the patients were enrolled through a convenient non-probability sampling technique. The sample size was calculated with the mean BNP levels in patients with severe MS i.e. 144.3±83.9 pg/ml (10), d=20%, and 95% confidence interval the calculated sample size was 68 patients.

The inclusion criteria for this study was all the patients having age more than 25 years and less than 70 years, moderate to severe MS of either gender, and given informed & written consent before enrollment. Patients with left ventricular dysfunction (EF <55%), documented coronary artery disease, acute on-going myocardial ischemia, chronic hypertensive patients, hypertrophic cardiomyopathy, concomitant moderate to severe regurgitant or stenotic lesions other than mitral stenosis, patient had history of valve replacement/repair, chronic renal failure, renal impairment (Creatinine clearance <60 ml/min), and pregnant women were excluded from this study.

The study was conducted after approval from the ethical committee of the Institute. Patients of either gender with age 25 to 70 years reported to adult cardiology department, NICVD for the follow up of diagnosed MS were enrolled in the study after keeping in view the inclusion & exclusion criteria. An informed consent was obtained after explaining purpose & procedure of the study. Patient's clinical history and examination were done by principal investigator. Diagnosis of RHD was made using Revised Jones Criteria (11). A documented proof of echocardiography was used for the diagnosis and quantification of mitral stenosis disease severity. Blood samples were collected by venipuncture from a peripheral vein and sent to laboratory for serum BNP analysis without any delay within 30 minutes. No additional cost was charged to the patients. All data were recorded on a pre-designed Proforma that was comprised

of demographic features, clinical history, echocardiographic features of MS severity, and Laboratory investigations.

DATA ANALYSIS PROCEDURE:

Data were entered in SPSS version 22 for the analysis. Mean and standard deviation were calculated for quantitative variables such as age, mitral valve area (MVA), pressure half-time (PHT), pulmonary artery systolic pressure (PASP) and serum BNP levels. Frequencies and percentages were calculated for qualitative variables like gender, diabetes mellitus, hypertension, categorization of age & BNP levels, and moderate/severe MS. Stratification was done on age and gender to minimize the effect of confounders, post stratification t-test was applied taken $p \leq 0.05$ as significant.

RESULTS:

The overall mean age of study subjects was 42.21±11.50 years, with range of 35 (25 − 70) years. Among them, majority were females 43 (63.2%). The age was stratified in two groups. 33(48.5%) patients were in ≤42 years age group (group I) and 35(51.5%) patients were in >42 years age group (group II). The serum BNP level was stratified in two groups. BNP Level of 33(48.5%) patients was ≤700 pg/ml and 35(51.5%) patients had BNP level >700 pg/ml. Table no.: 01. The overall mean serum BNP level was 1071.12±807.26 pg/ml, with range of 2426 (168 − 25941) pg/ml. Graph No.: 01.

The mean BNP-levels were slightly higher in male 1094.92±800.43 pg/ml as compare to female 1057.28±820.31 pg/ml, respectively. The gender distribution with respect to BNP level groups

are presented in Graph No. 02. Similarly, patients having age more than 42 years had higher levels of BNP as shown in Graph No. 03.

Finally, it was observed that mean difference of serum BNP level was highly significant among patients with severe mitral stenosis as compared to moderate mitral stenosis with $p<0.01$. Table No. 02.

DISCUSSION:

Rheumatic heart disease (RHD) is particularly and disproportionally a disease of low and middle income countries (LMICs) such as Pakistan and approximately 33 million people are living with RHD worldwide with 80% are from LMICs hence making it the global health problem. The mortality rate associated with this disease ranges up to 275,000 deaths per year and among them 95% are from LMICs. The most common complications associated with this disease are development of heart failure, acute rheumatic fever, infective endocarditis, atrial fibrillation, cerebrovascular accident, and valvular heart disease including mitral stenosis (12). In patients with chronic rheumatic heart disease, mitral valve involvement observed in more than 50% of the patients and around 20% of the patients experience combine lesion in mitral and aortic valve. While, tricuspid valve is the least affected valve and accounts for only 10% (13).

N-terminal pro-BNP releases in response to chronically increased pressure in the ventricles such as in ventricular dysfunction or heart failure. Its role in heart failure is well defined (14-16) but its direct association in patients with mitral stenosis is not well defined in the presence of normal left ventricular function (LV). The release of BNP in patients with mitral stenosis with normal LV function is probably the result of volume and pressure overload particularly when the disease is of moderate to severe intensity that is why its significance is not well studied yet. Observations

from our study has shown that more than >50% of the patients with mitral stenosis tend to have higher levels of pro-BNP (>700 pg/mL, cut off is 400 pg/mL) with a mean value was 1071.12±807.26 pg/mL. on the other hand, severity of mitral stenosis has a significant association with the levels of pro-BNP, as shown in our results i.e. patients with severe mitral stenosis tend to have higher pro-PNP levels as compare to patients with moderate mitral stenosis, 1466.70±772.76 and 390.72±107.72, respectively. Data is limited to authenticate our findings on a larger scale but few smaller studies have shown some association. In a study conducted by Eryol NK (10) and colleagues have shown similar association as we have observed in our study but levels of pro-BNP in their study far less than our study in patients with moderate to severe mitral stenosis and also they had male predominance while our study had female predominance. Low levels of pro-BNP in their study could probably due to their inclusion of mitral stenosis cases of mild intensity also in which level of pro-BNP either normal or very mildly elevated. Due to this factor we have excluded patients with mild mitral stenosis. The findings of our study are also consistent with the previously conducted case control study by the Mazurkiewicz L et al in 2017 (5).

Some of the previously conducted studies have also shown the association between basic demographic characteristics such as age, gender, pulmonary artery systolic pressure, and blood pressure (17-19). However, there was not any difference in terms of these factors, which, in our opinion, will enable us to better assess the possible relationship between MS and plasma BNP levels.

STUDY LIMITATIONS.

A limitation of our study was that female gender predominated in our study. Therefore, one should be cautious in extrapolating our findings to men with raised serum BNP levels. One of the limitations in this study is that it was an observational study in which one cannot prove cause and effect of MS, its treatment, and worse outcomes. The study was conducted on a small scale and at urban environment therefore, the findings might not be generalizable to larger populations.

CONCLUSION:

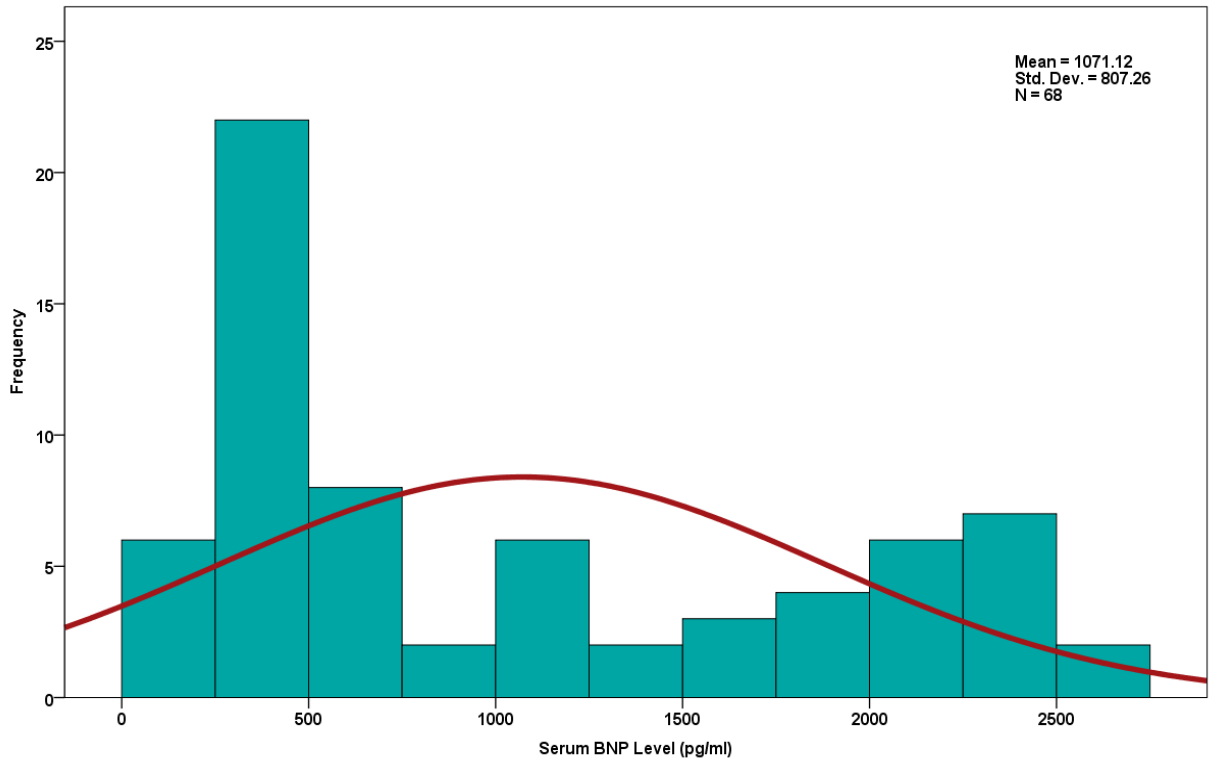
In conclusion, the mean BNP levels were significantly higher in patients with severe Mitral Stenosis and is more common in females than males. Further studies focusing on the male gender, underlying comorbid conditions and other clinical parameters such as right cath findings should be included to further elaborate the results of our study.

Table No. 01: Baseline and Clinical characteristics of study subjects (N = 68)

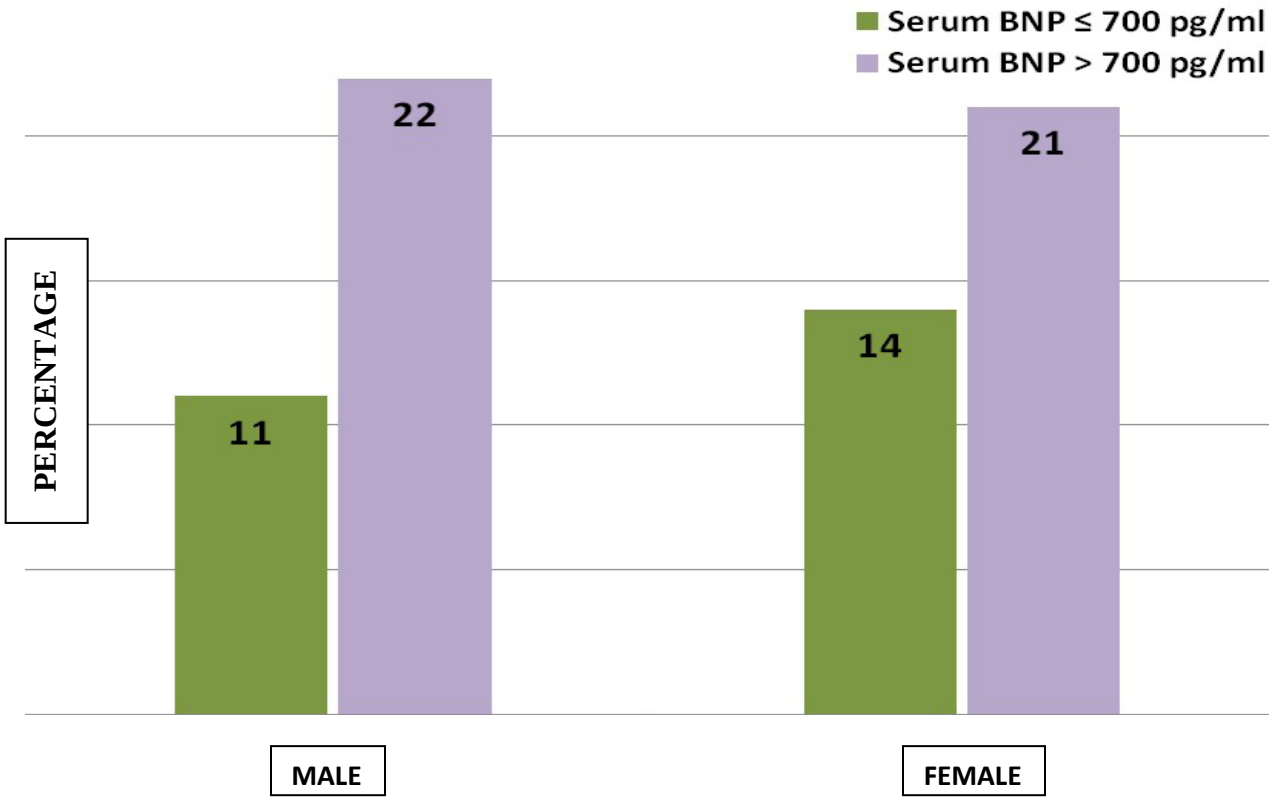
Baseline Variables		
Age – Years		
Range	25 - 60	
Mean±SD	42.21±11.50	
Group I (<42 years)	33	48.5
Mean±SD	31.82±5.63	
Group II (≥42 years)	35	51.5
Mean±SD	52.00±5.21	
Gender		
Male	25	36.7
Female	43	63.2
Area of residence		
Urban	48	70.5
Rural	20	29.4
Marital Status		
Single	5	7.3
Married	60	88.2
Widow	3	4.4
Comorbids		
Diabetes Mellitus	12	17.6
Hypertension	18	26.4
Clinical Parameters		

Mitral Valve		
Planimetric MVA, mean±SD - cm2	1.28±0.39	
Pressure half-time – msec	148.97±26.79	
Pulmonary Artery Systolic Pressure, mean±SD	58.09±10.03	
Severity of Mitral Stenosis		
Moderate	25	36.7
Severe	43	63.2
BNP-Level – pg/mL		
≤700	33	48.5
>700	35	51.5

Graph No. 01: Serum Pro-BNP Levels



Graph No. 02: Comparison of gender with levels of Pro-BNP



Graph No. 3: Comparison of age groups with levels of Pro-BNP

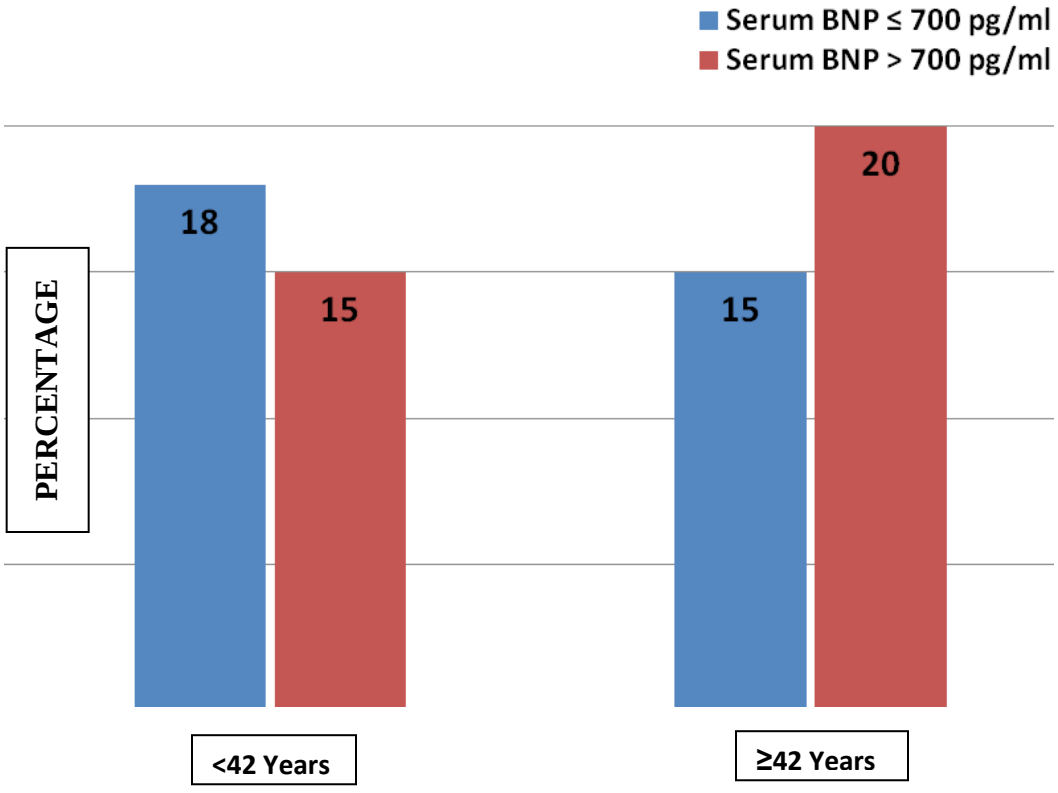


Table No. 02: Descriptive statistics of BNP levels according to severity of mitral stenosis (N = 68)

BNP Levels parameters - pg/mL	Severity of Mitral Stenosis		
	Moderate (N = 25)	Severe (N = 43)	p value
Mean±SD	390.72±107.72	1466.70±772.76	0.001*
95% CI	346.25 – 435.19	1228.88 – 1704.52	
Median (IQR)	399.0 (176)	1661 (1441)	
Range	375	2396	
Minimum	168	198	
Maximum	543	2594	

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