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ORGINAL ARTICLE

Prognostic Value of Serum BNP in Patients with NSTEMI and Its Correlation with Extent of Coronary Artery Disease

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ABSTRACT

Background: BNP biomarker is found to have a positive correlation to coronary artery disease (CAD). So it may have diagnostic and prognostic valu e. **This study aims** to predict the prognostic value of serum BNP level as a biomarker and the severity and complexity of CAD in nnon-ST-elevationmyocardial infarction (NSTEMI) with normal left ventricular (LV) systolic function (preserved ejection fraction) as regards both SYNTAX score and GRACE score. We enrolled patients who presented with NSTEMI and normal LV systolic function (LV EF ≥50Grace'srace score was calculated. All patients underwent BNP analysis, echocardiography, and coronary angiography within 24 to 72 hours of admission. SYNTAX score was calculated.

Results: Sixty-four patients with NSTEMI with a mean GRACE score 140.41 ±28.5 and a mean SYNTAX score of 17.39 ±9.8 were enrolled. BNP level was 135.17 ±37.9ng/dL. According to the level of serum BNP, Patients were divided into 2 groups, the first group with high BNP (>80 ng/dl) and second group with low serum BNP level. The results showed significant differences between both groups regarding the GRACE score (p =0.001) and SYNTAX score (p =0.001).Also, there were significant positive correlations between BNP and age (p =0.001), Grace score (p =0.001), and SYNTAX score (p =0.001). At a cutoff of 141pg/dL, the BNP yielded a sensitivity of 83% and specificity of 75% for the prediction of SYNTAX score of more than 32.

Conclusion: Serum BNP level as a biomarker provides independent prognostic value in NSTEMI patients. Patients with high serum BNP levels were more likely to have higher GRACE and SYNTAX scores. Serum BNP level had good diagnostic accuracy in predicting SYNTAX score.

Key Words: BNP; NSTEMI; Grace; Syntax; Coronary artery disease.

INTRODUCTION

Every year, approximately fifteen million people are admitted to the emergency unit in USA and Europe, with symptoms suggestive of acute coronary syndrome (ACS) **[1]**. Despite lifestyle measurements and modifications and interventions, CVD still remains a major problem. For this issue, the need for prevention and detection of CAD early as possible by using newer and more cost-effective friendly tools are suggested **[2]**.

The character of ACS is very complicated course and it has different physiopathological mechanisms, for example, plaque rupture with acute thrombosis, mechanical obstruction with the progressive process, unstable angina with secondary causes, inflammation, and intermittent obstruction (coronary vasospasm) **[3]**.

In acutely ill cardiac patients, adding cardiac biomarkers to the diagnosis and the treatment will integrate all. At the first, the description of atrial natriuretic peptide (ANP), was understood by the endocrine nature of the heart, and then later detection of brain (B-type) natriuretic peptide (BNP), which is mainly released from the myocardium in humans **[4]**.

The measurements of the natriuretic peptide are useful and beneficial for risk stratification irrespective of the cause during admission time or during hospital stay course. We can quantifying the severity of heart failure by measuring Natriuretic peptide concentrations and this also aid to predict the mortality either short or long term **[4]**. The

abnormalities in diastolic and systolic functions as well as myocardial ischemia release NPs. BNP and NT-proBNP values are powerful prognostic markers in patients diagnosis as acute coronary syndromes **[4]**.

The SYNTAX score is a good anatomical assessment tool for coronary vasculature. This score grades also the complexity of coronary artery disease **[5]**.

OBJECTIVES

Our study aimed to predict the prognostic value of serum BNP level as a biomarker and complexity and severity of coronary artery disease in non ST-elevation myocardial infarction with normal left ventricular systolic function as regards both SYNTAX score and GRACE score.

METHODS

Our study had been carried out in cardiology department; Zagazig University.

Our study was cohort prospective study, at 80% power and 95% CI and included (64) patients with non ST- segment elevation myocardial infarction (NSTEMI).The involved patients with NSTEMI was diagnosed when the patient complained of acute chest pain associated with raised troponin-I values (>1.0 ng/mL in any sample during the first 9 h after admission) with or without ST/T changes in the ECG, without any other obvious cause for this chest pain **[6]** .The included patients divided them into two groups; first group with high BNP (>80 ng/dl) and second group with low serum BNP level (< 80 ng/dl). **[7]**,and correlated with clinical variables, Grace and Syntax scores.

Inclusion Criteria

Patients presented with acute chest discomfort but no persistent ST-segment elevation [non-ST-segment elevation ACS (NSTEACS)] exhibit ECG changes that might include transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves, or pseudo normalization of T waves; or the ECG may be normal., and also when an elevation of troponin-I levels (>1.0 ng/mL in any sample during the first 9 hours post-admission) occurred, in the absence of any other demonstrable cause for the chest pain **[8]**. And also those with preserved left ventricle systolic function. (Estimated EF ≥ 50%).

Exclusion criteria

Based on patient history, physical examination, ECG and echocardiography, we excluded patients suffered from the following: Any contraindication for angiographic study or decision for conservative treatment. And patients with significant valvulopathy or associated with heart valvular disease. Also we excluded patients with kidney diseases or impairment which defined as estimated creatinine clearance < 50ml/min, calculated by use of the Cockroft-Gault9 formula. Patients with left ventricular dysfunction (EF≤50% by Simpson's rule), either symptomatic or not, clinical signs or symptoms of heart failure, current major liver diseases and obese patients. (Considered as a BMI of >/30kg/m2) were excluded. We excluded patients had recent surgery or major trauma. Also patients had history of previous ST elevation myocardial infarction or history of CVS (Cerebrovascular stroke) were excluded from our study. Patients with Inflammatory conditions or recent infection or suffered from malignancy or under its treatment were excluded. And any patient suffered from congenital heart diseases excluded.

Ethical consideration:

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All patients were subjected to:

Clinical and laboratory evaluation:

History taking and complete physical examination for the following data:

Demographic data as (age, gender).

Patients had risk factors for IHD (clinical variables):

Hypertension was defined according to the criteria of the 2013 ESH/ESC Guidelines. Persons were considered hypertensive if 2 or more blood pressure readings were greater than or equal to 140mm Hg systolic and/or 90mm Hg diastolic or if the patient is already diagnosed as hypertensive and on regular antihypertensive drugs to control his blood pressure **[9]**.

Diabetes mellitus, was defined according to the ADA criteria (HbA1C ≥6.5% or FPG ≥126 mg/dl or 2-h plasma glucose ≥200 mg/dl) or if the patient has a history of diabetes and still on medical treatment **[10]**.

Smoking, Smokers were defined as those who reported daily smoking. Both ex-smokers and occasional smokers were considered as nonsmokers.

Dyslipidemia, was defined according to the ATP III definition, which was determined by one or more of

the following criteria: total cholesterol more than 200 mg/dL, low density lipoprotein cholesterol (LDL) more than 130 mg/dL, high-density lipoprotein-cholesterol (HDL) ≤ 40 mg/dL in males and ≤ 50 mg/dL in females and triglycerides ≥150 mg/dL or the use of anti-dyslipidemia drugs**. [11]**

Obesity, which was defined by calculating the body mass index (BMI) (Weight in kilograms/height in meters squared). Overweight was considered as a BMI of 25 to 29.9 kg/m2; obesity was considered as a BMI of >/30kg/m2 and severe obesity was considered as a BMI ≥40kg/m.

General and local cardiac examination for: Heart rate count, measurement of blood pressure, body mass index, and any signs of cardiac decompensation presented or not (rales, gallop. pulmonary congestion).

12 lead ECG on admission and 8 hourly on the first 24 hours then daily. With special concern for, characteristic abnormalities include, ST-segment depression, transient ST-segment elevation, and T-wave changes.

The GRACE risk score for the patient was calculated by online risk model.

Cardiac Troponin: as noted by elevation of Troponin-I level. Initial samples were checked at presentation and if initial biomarkers were negative, it were measured again within 6 hours of symptom onset. They were re-measured within 8-12 hours after symptom onset. For measurement of plasma troponin-I, immunofluorescence assay (Dade-Behring) was used, with analytic sensitivity of 0.1 ng/ml and the upper limit for MI diagnosis was 1.0 ng/ml.

Routine laboratory investigations with special concern to:

Renal function test (blood urea, serum creatinine level), Complete Blood Count, liver function test, blood sugar including HbA1C and lipid profile.

Blood sample analysis for BNP was performed within 72 to 96 hours of hospital admission. For BNP analysis, 6 ml of a peripheral vein blood was taken and disturbed in tubes, within the first 72 hours of hospital admission. The quantitative immunofluorescence assay (Beckman coulter, USA) was immediately used for Plasma BNP analysis.

Imaging:

Plain chest X-ray.

All patients underwent **transthoracic echocardiography,** for assessment of the LV function by measuring ejection fraction, (Standard views were assessed in left lateral position using **GE VIVID 8** echo machine). All studies were performed during the index hospitalization within 72 hours after the onset of the myocardial infarction.

Angiographic analysis:

Coronary angiography and left cardiac catheterization were performed, for assessment of coronary anatomy and lesions, standard angiographic projections were used to minimize foreshortening. The radial access was considered in all cases unless if there was other concerns. And then the timing of invasive strategy was classified into:

An immediate invasive strategy (<2hours), was recommended in patients with at least one of the following very high-risk criteria:

Any patient had cardiogenic shock or signs of hemodynamic instability.

Patient suffered from recurrent or refractory chest pain despite medical treatment.

Any patient had malignant arrhythmia or life-threating arrhythmias.

Any patient had mechanical complications as sequale of MI complications.

Any patient developed heart failure clearly related to NSTE-ACS complication.

ECG findings as the presence of ST-segment depression >1mm in≥ 6 leads additional to ST-segment elevation in aVR and/or V1.

An early invasive strategy within 24 hours was recommended in patients with any of the following high-risk criteria:

Any patient diagnosed as NSTEMI and this suggested by the diagnostic algorithm recommended.

ECG findings like, dynamic or presumably new contiguous ST/T-segment changes suggesting ongoing ischemia (symptomatic or silent).

Presence of transient ST-segment elevation in 12 leads ECG **[11-12]**.

GRACE risk score >140 **[13]**.

Selective invasive strategy: Patients with no recurrence of symptoms and none of the very high or high-risk criteria mentioned in the recommendation above and regarding the timing of invasive strategy are to be considered at low risk of short-term acute ischemic event, and appropriate ischemia testing or detection of obstructive CAD by CCTA was recommended **[14-15]**.

Then all coronary angiograms results were evaluated according to the SYNTAX score by which we can grades the complexity of coronary artery disease and consider a good anatomical assessment

tool for coronary vasculature. The calculation of the SYNTAX score can be done by summation of the points given individually to each identified lesion with >50% stenosis in vessels >1.5 mm in diameter **[16].**

In-Hospital Management: All patients received:
Loading dose Aspirin (ASA) 300 mg.
Unfractionated Heparin (UFH) guided by activated clotting time (ACT 300-350 second).

Clopidogrel (600 mg as a loading dose then 75 mg as a maintenance dose).
Conventional treatment {Beta Blockers, Nitrates, ACEI & Statins}. Specific medications and doses were left to the treating physician.
In hospital Major adverse cardiac events (MACE) were also recorded (as death, malignant arrhythmia, reinfarction and hear failure).

Operation design:

Type of study:

This study was a cohort prospective study. It included patients with (NSTEMI) which included Mean of single vessel involved =23.09 and standard deviation=15.34 and variance 235.316 **(Results from Open EPI, Version 2).**

The primary outcome endpoints of the patients were followed up during their in-hospital stay. Adverse cardiac events were followed up, included heart failure, cardiogenic shock, need for cardiopulmonary resuscitation, mechanical complications, serious ventricular arrhythmias, myocardial re-infarction, and the need for target vessel revascularization, CVA and death.

Administrative design:

Approval was obtained from Institutional Review Board (IRB).

STATISTICAL ANALYSIS

Was performed using statistical package for the social science (SPSS) program version 20(SPSS, Chicago, IL, USA).Continuous variables were expressed as mean and standard deviation, while categorical variables were expressed as numbers and percentages. Comparison of continuous variables among groups was made using the student's t-test.Associations between two categorical variables were tested using the likelihood ratio x^2 test, as appropriate. Statistical correlation between continuous variables was tested using the Pearson's product-moment coefficient of correlation(r).All tests of significance were two-tailed and a p-value < 0.05 was considered statistically significant-value <0.001 was considered highly statistically significant and p-value ≥ 0.05 was considered non-statistically significant.

RESULTS

Demographic Characteristics

In the present study, we included 64 adult patients with NSTEMI. Notably, the majority of patients were males (68.8%) with a mean age of 57.34 ±10.86 years. Forty-four percent of the patients were smokers. Almost 70% of the patients had hypertension, 53% had diabetes, and 75% had dyslipidemia. Fourteen (21.9%) patients had family history of CAD and only 3 patients had previous PCI**. (Table 1)**

The mean Grace score of the included patients was 140.41 ±28.5 and the mean SYNTAX score was 17.39 ±9.8 (**Table 2).**

The mean cardiac troponin level of the included patients at admission was 1.65 ±3.6ng/dL and the peak troponin level was 21.08 ±21.5ng/dL**.**
The mean BNP level was 135.17 ±37.9ng/dL. Almost 53% of the patients had high BNP level **(Table 3)**.

Difference:

Regarding the difference between low and high BNP according to different risk factors **(Table 4)**. There were statistically significant differences between both groups in age (p =0.004) and the presence of DM (p =0.005). On the contrary, there were no statistically significant differences between both groups regarding gender (p =0.52), HTN (p=0.9), dyslipidemia (p =0.56), and history of PCI (p =0.24).

There was statistically significant difference between both groups of low & high BNP level regarding SBP (p =0.016). However, this differences was insignificant between both groups in terms of HR (p =0.069) and EF (p =0.184).

Concerning the difference between low and high BNP in the aspect of Grace and Syntax Score, there were statistically significant differences between both groups regarding Grace Score (p =0.001) and SYNTAX score (p =0.001) **(Table 5)**.

Correlation:

After doing the correlation between the BNP and clinical variables, there were statistically significant positive correlations between BNP and age (p =0.001), Grace score (p =0.001), and SYNTAX score (p =0.001) **(Table 6).**

Regression Analysis:

Table 7 shows the area under the curve and the diagnostic accuracy of BNP. At a cutoff of 141pg/dL, the BNP yielded a sensitivity of 83% and specificity of 75% for prediction of SYNTAX score of more than 32 **(Figure 1)**.

Table (1): Shows the baseline demographic and clinical characteristics of the included patients

Variables	**Patients (N =64)**	
	No	%
Age Mean ±SD Median (IQR)	 57.34 ±10.4 57 (49 – 63)	
Gender		
Male	44	68.8
Female	20	31.3
Hypertension		
Yes	45	70.3
No	19	29.7
DM		
Yes	34	53.1
No	30	46.9
Smoking		
Yes	28	43.8
No	36	56.3
Dyslipidemia		
Yes	48	75.0
No	16	25.0
Previous PCI		
Yes	3	4.7
No	61	95.3
Family History		
Yes	14	21.9
No	50	78.1

Table (2): The risk scores of the included patients

Variables	**Patients (N =64)**	
	No	%
Grace Score		
• Mean ±SD	140.41 ±28.5	
• Median (IQR)	138 (122.5 -154)	
Syntax		
• Mean ±SD	17.39 ±9.8	
• Median (IQR)	15 (9 -25)	

Table (3): The lab results of the included patients

Variables	**Patients (N =64)**	
	No	%
Trop Admission		
• Mean ±SD	1.65 ±3.6	
• Median (IQR)	0.45 (0.13 -1.95)	
Trop Peak		
• Mean ±SD	21.08 ±21.5	
• Median (IQR)	14 (5.05 -29.4)	
BNP level		
• Mean ±SD	135.17 ±37.9	
• Median (IQR)	97.8 (36.9 -166.98)	
BNP category		
• BNP < 80	30	46.9
• BNP > 80	34	53.1

Table (4): Shows the difference between low and high BNP regarding different risk factors & clinical signs.

Variable	**BNP <80(N =30)**	**BNP >80 (N =34)**	**MW test or X^2**	**P-value**
Age				
Mean ±SD	53.17 ±9.1	61.03 ±10.2	293.5	**0.004**
Median (range)	52.5 (37 – 72)	61 (43 – 84)		
Gender, No. (%) **Female** **Male**	 21(70%) 9 (30%)	 23 (67.6%) 11 (32.4%)		0.52
HTN, No. (%)	21 (70%)	24 (70.6%)		0.99
DM, No. (%)	10 (33.3%)	24 (70.6%)		**0.005**
Dyslipidemia, No. (%)	24 (80%)	24 (70.6%)		0.56
History of PCI	0	3 (8.8%)		0.24
HR (BPM)				
Mean ±SD	65.93 (8.2)	71.15 (12.2)	375.500	0.069
Median (range)	65 (47 – 85)	70 (50 – 100)		
SBP (mmHg)				
Mean ±SD	125.9 (13.3)	138.67 (24.8)	332.000	0.016
Median (range)	130 (120 -140)	130 (120 -170)		
EF (%)				
Mean ±SD	57.37 (4.1)	55.77 (5.4)	414.000	0.184
Median (range)	58 (50 – 65)	55 (50 – 60)		

Table (5): Shows the difference between low and high BNP according to Grace and Syntax Score

Variable	BNP <80 (N =30)	BNP >80 (N =34)	Mann-Whitney test	P-value
Grace score				
Mean (SD)	125.03 (23.9)	153.97 (25.3)	204.500	<0.001
Median (Range)	130.5 (37 – 157)	147.5 (110 – 213)		
SYNTAX score				
Mean (SD)	12.63 (7.6)	21.72 (9.6)	230.00	<0.001
Median (range)	12 (2 – 27)	23 (6 – 40)		

Table (6): Shows the correlation between the BNP and clinical variables

Variable	BNP level
Age	
Correlation Coefficient (r)	0.520
P-value	**<0.001**
SBP	
Correlation Coefficient (r)	0.174
P-value	0.170
EF%	
Correlation Coefficient (r)	0.005
P-value	0.967
Grace score	
Correlation coefficient (r)	0.600
P-value	**<0.001**
SYNTAX	
Correlation coefficient (r)	0.412
P-value	**<0.001**

Table (7): shows the area under the curve and the diagnostic accuracy of BNP. At a cutoff of 141pg/dL, the BNP yielded a sensitivity of 83% and specificity of 75% for prediction of SYNTAX score of more than 32 (Figure 1).

Table 7: Shows the area under the curve and the diagnostic accuracy of BNP

Variable	AUC, 95% CI	P- value	Cut-off points	Sensitivity	Specificity	PPV	NPV
SS ≥32	0.82.5 (0.7–94)	0.009	≥ 141 pg/dl	83%	75%	88.3%	78.5%

PPV: Positive predictive value; NPV: negative predictive value; AUC: area under curve; CI: Confidence interval.

DISCUSSION

Acute coronary syndrome (ACS) is one of the commonest global causes of mortality and morbidity. Non-ST-elevation myocardial infarction (NSTEMI) is a serious, life-threatening, presentation of ACS that is characterized by notably high rates of morality and complications. Promote, accurate, diagnosis and treatment of NSTEMI is critical for optimum outcomes. Both ECG and cardiac biomarkers are the mainstays in the evaluation **[17]**.

Despite the fact that cardiac enzyme troponin-I have important and a major role in diagnosis and management of NSTEMI,but unfortunately its use is limited by its inability to detect myocardial ischemia in patients without necrosis (troponin blind interval). Thus, the diagnosis of NSTEMI remains a diagnostic challenge and newer, accurate, diagnostic tools are still needed **[18]**.

B-type natriuretic peptide (BNP) is a well-established predictor of heart failure (HF) hospitalization and mortality in patients with HF and considered important biomarker for diagnosis, follow up and prognosis in heart failure patients . Previous trials conducted on high risk patients revealed controversial results about BNP and its

ability to predict worse cardiovascular outcomes including MI and stroke **[19]**.

We enrolled the patients in the present prospective study to assess the relation between serum BNP level and the severity of CAD in NSTEMI patients with preserved LV systolic function using both standard scores; the SYNTAX and GRACE scores.

Regarding the level of BNP of the included patients, we found that the mean BNP level was 135.17 ±37.9ng/dL. Almost 53% of the patients had high BNP level. There were statistically significant differences between high BNP and low BNP groups in terms of age (p =0.004) and DM (p =0.005). Patients with high BNP were significantly older and more likely to have DM.

In agreement and concordance with our findings, **Redfors and colleagues** found that patients with elevated BNP levels were older and more frequently had additional cardiovascular risk factors and lower LV ejection fraction than those with normal BNP **[20].**

Palazzuoli and colleagues found a positive between BNP and the extension of coronary lesions using Gensini Score in patients with both stable angina and ACS without ST-elevation **[21]**.

In another study, **Palazzuoli and colleagues** evaluated circulating BNP levels in patients with NSTEMI and preserved systolic function, BNP was positively correlated to hypercholesterolemia and diabetes **[22]**.

On the contrary to our findings, **Goyal and colleagues** aimed to assess the relation between serum BNP values and the severity of CAD. A total of 197 patients with ACS without ST elevation with normal LV systolic function were enrolled. There were no statistically significant differences between high and low BNP groups in terms of age and DM**[7]**.

Really, the exact and definite cause of such discrepancies in the reported results in the published literature is unclear. However, these discrepancies can be attributed to the substantial methodological differences between different studies; studies varied greatly in terms of sample size and duration of follow-up.

the GRACE score was recommended and considered routine and important tool for stratifying the risk in ACS and quickly applied to use it in clinical practice **[23]**.

In the present study, we found that there was a statistically significant difference between high and low BNP groups in terms of Grace score (p =0.001). In addition, there was a statistically significant positive correlation between BNP and Grace Score (p =0.001).

In concordance with our findings, **Sinclair and colleagues** recruited 142 unselected patients with ACS. BNP was measured and patients were stratified according to BNP and GRACE scores. Elevated BNP significantly predicted the increase in GRACE score **[24]**.

Similarly, **Ang and colleagues** enrolled 449 ACS patients and both GRACE score and bedside BNP levels were measured at the admission time. It is noticed that both higher GRACE parts and higher BNP parts predicted cardiovascular events. There was a positive correlation between the GRACE score and serum BNP level($R = 0.552$, $p<0.001$) **[25]**.

Tzikas and colleagues noticed that the BNP level has a strong association and adds predictive value beyond the GRACE risk score in patients presenting with a suspected AMI. They found a significant correlation between the GRACE score and serum BNP level **[26]**.

By applying the SYNTAX score, patients with complex CAD with high (≥33) or intermediate (23–32) scores get more benefits with CABG, whereas PCI remains a good option for those with a less complex lesion (SYNTAX score ≤22) **[27].**

In the current study, we found that there was a significant difference between high and low BNP groups in terms of SYNTAX score (p =0.001). There was a statistically significant and also positive correlation between BNP and SYNTAX score (p =0.001).

The most eminent result in the current study is the determination of a cutoff value of 141pg/dL of the BNP that yielded a sensitivity of 83% and specificity of 75% for the prediction of a SYNTAX score of more than 32.

In concordant with our results, **Mahmoud and colleagues** studied the relationship between serum BNP value and CAD severity in patients with NSTEMI and preserved LV systolic function using the SYNTAX score. The levels of BNP were positively correlated with the degree of SYNTAX score (r = 0.78) **[28]**.

Similarly, **Tasar and colleagues** aimed to evaluate the role of BNP in assessing CAD complexity by SYNTAX score in a prospective study among ACS patients. A high BNP could independently predict a high SYNTAX score **[29]**.

Romel and colleagues used another score to evaluate the importance of BNP in predicting the

severity of CAD in ACS and NSTEMI patients, They found that there was a linear correlation between BNP pg./ml and CAD severity in terms of Vessel score (r=0.38, p=0.01) and Friesinger score (r=0.51, p=0.01) **[30]**.

CONCLUSION

BNP provides independent prognostic value in NSTEMI. Patients with BNP levels above 80pg/dL were more likely to have higher both GRACE and SYNTAX scores. In addition, the BNP level had good diagnostic accuracy in predicting the SYNTAX score.

RECOMMENDATIONS

- BNP provides independent prognostic value in NSTEMI. These findings are very important as it confirms the need for continuous monitoring of BNP levels in patients with NSTEMI to predict patients with poor outcomes.
- Nevertheless, supplementary studies with strict design, good numbers of patients enrolled and many centers should share in the study, all of these recommendations are required.

LIMITATIONS:

- the small sample size is the main limitation of our study, however, our sample was carefully defined and selected based on clinical and echocardiographic criteria.
- The study was limited to one center only and therefore the results cannot be generalized to the general Egyptian population.
- The descriptive nature of the present study may also preclude the conclusion of association analysis.

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Conflict of interest: We report no competing interest associated with the work reported in this manuscript.

Ethics approval and consent to participate: Approval was obtained from Zagazig University Institutional Review Board (IRB). (Approval n. 1656/9-3- 2015). All patients gave written informed consent.

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