

## LEVELS OF "N TERMINAL- PRO BRAIN NATRIURETIC PEPTIDE" (NT-proBNP) AND ASSOCIATED RISK FACTORS IN SYSTOLIC HEART FAILURE CONSEQUENTIAL TO ISCHAEMIC HEART DISEASE

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### ABSTRACT

#### BACKGROUND

Early identification of Heart Failure as a post MI complication is very important in a clinical setting. Particularly in a resource strapped environment such as a centre in a remote district. Our study aims to study levels of NT-pro BNP in Systolic Heart Failure consequential to Ischaemic Heart Disease, the correlation between the levels of NT-pro BNP and Systolic Heart Failure consequential to Ischaemic Heart Disease and study the risk factors in patients presenting with Heart Failure consequential to Ischaemic Heart Disease and their correlation to NT-proBNP Levels if any is present.

#### MATERIALS AND METHODS

100 patients admitted into Basaveshwar Teaching and General Hospital Attached to M.R. Medical College diagnosed with Systolic Heart Failure (Ejection Fraction <40%) after Ischaemic Heart Disease. A previously designed proforma was used to collect data on cases admitted complete detailed history and clinical examination was taken and performed NT-PRO BNP, Troponin I, Echocardiography, ECG were performed. The data collected was then made into a chart and subjected to statistical analysis. There was no long term or short term follow up of the patient.

#### RESULTS

In the cohort studied the NT-PRO BNP levels Ranged between 358 pg/ml - 3000 pg/ml With Mean Value of 2049.93 pg/ml Median Value of 1886 pg/ml. of the cohort 72% were male and 28% were female and the 64% of the total population who were smokers lead to a significant relationship between NT-Pro BNP and smoking ( $p < 0.05$ ). While we managed to prove that the NT-Pro BNP values had a good predictive value for heart failure ( $p < 0.05$ ) we also recognise the need to further expand the study towards a larger population as well as include more criteria.

#### CONCLUSION

NT-PRO BNP is a good predictor of heart failure in settings of acute mi. NT-PRO BNP is a good tool for risk stratification of acute mi patients so that appropriate treatment can be planned. NT-PRO BNP can be used in an acute setting as well and can accurately predict heart failure in the absence of echocardiography, hence can be used in remote areas as a good tool.

#### KEYWORDS

N Terminal - pro Brain Natriuretic Peptide (NT-pro BNP), Left Ventricular Systolic Heart Failure, Ischemic Heart Disease.

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#### BACKGROUND

Coronary artery disease (CAD) and its result, myocardial infarction (MI) continue to be a significant cause of mortality and morbidity in the world. Over the past 50 years, it has become clear that the cascade of thrombotic events following atherosclerotic plaque rupture causes occlusion of

the coronary artery, interrupting blood supply and oxygen to myocardium thus resulting in infarction.

Myocardial necrosis following infarction is followed by many known complications of which Heart Failure is a very important one. Early treatment of myocardial ischemia to prevent necrosis with treatments such as fibrinolysis, coronary artery bypass grafting and percutaneous coronary intervention has improved outcome.<sup>1</sup>

Optimal risk stratification of patients with acute myocardial infarction is of paramount importance to deliver appropriate care. Risk prediction based on clinical, Electrocardiography (ECG), and biochemical i.e., cardiac troponin, Creatinine Kinase-MB, however is relatively inaccurate.<sup>2</sup>

Brain natriuretic peptide (BNP) is a circulating cardiac hormone released mainly from the ventricles in response to

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myocyte stretch. The measurement of BNP has been shown to be useful in detecting LV dysfunction, particularly after Acute Myocardial Infarction (AMI), and to be related to poor outcome.<sup>1</sup> Elevated levels of BNP and N-terminal pro-BNP (NT-pro BNP) may indicate the extent or severity of the ischaemic insult correlating with adverse outcomes.<sup>2</sup>

Many of the studies have<sup>2</sup> concentrated on the role of NT-pro-BNP levels in predicting the long-term morbidity and mortality of AMI.

This study intends to determine the relationship between NT-pro-BNP levels, the risk factors leading up to the event and heart failure as a complication of acute ST segment elevation myocardial infarction (STEMI) and the role of NT-pro-BNP in predicting the short-term outcome of acute STEMI.

### Objectives of the Study

The main objectives of the study were

- To study levels of NT-pro BNP in Systolic Heart Failure consequential to Ischaemic Heart Disease.
- To study the correlation between the levels of NT-pro BNP and Systolic Heart Failure consequential to Ischaemic Heart Disease
- To study the risk factors in patients presenting with Heart Failure consequential to Ischaemic Heart Disease and their correlation to NT-proBNP Levels.

### MATERIALS AND METHODS

It was a cross sectional study conducted in the Department of Medicine, Basaveshwar Teaching and General Hospital (Kalburgi), during the period from December 2014 to August 2015 in which 100 patients who presented with acute ST elevation myocardial infarction were included. A thorough history was recorded and thorough general and systemic examination was carried. ECG, cardiac troponin I, Urea, creatinine, NT-pro BNP at the time of admission and Echocardiography within 7 days of admission were done.

#### Sampling – NT-proBNP

Sample volumes of 150 µL of venous blood were collected in heparinised vials and assayed using the Roche cardiac pro BNP test kits in Cobas-H 232 instrument. This test is an immuno-assay. It contains one monoclonal and one polyclonal antibody directed against NT-proBNP and has a measuring range of 60-3000 pg/ml.

#### Sampling – Cardiac TROP I

Sample volumes of 150 µL of venous blood were collected in heparinised vials and assayed using the Roche cardiac troponin quantitative test kits in Cobas-H 232 instrument.

#### Echocardiography

All patients were subjected to a detailed echocardiography (Echo) and Doppler evaluation. Qualitative and quantitative assessment of segmental and global LV function was done in all patients with Vivid S5 High Performance Echocardiography machine by Hitachi Medical systems. Modified Simpson's technique was used to determine the

end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF). EF of <40% was taken as abnormal.

### Inclusion Criteria

Cases having

- Typical ischaemic symptoms and ST segment elevation of at least 1mm in 2 or more ECG leads.
- Admitted within 12 hours after onset of symptoms.
- Patients within the age group of 30-80 years.
- All patients diagnosed with Systolic Heart Failure (Ejection Fraction <40%) after Ischaemic Heart Disease.

### Exclusion Criteria

- STEMI patients with previous chronic heart failure.
- STEMI patients with previous chronic kidney disease.
- STEMI patients with cardiogenic shock at presentation.
- STEMI patients who present 12 hours after the onset of symptoms.
- STEMI patients of age <30 years or >80 years.
- Patients with non-ST segment elevation MI and unstable angina.
- Patients who present with Heart failure with preserved Ejection Fractions.
- Patients who present with Heart Failure consequential to any other aetiology other than Ischaemic Heart Disease, such as Rheumatic Heart Disease, Restrictive Cardiomyopathies, Cor-Pulmonale, Endo-Myocardial Disorders, etc.
- Patients with any other known causes which lead to elevated NT-pro BNP levels such as Chronic and Acute Kidney injuries, Acute Pulmonary Embolism, Primary or Secondary Pulmonary Hypertension, COPD, Respiratory Failure, Hyperthyroidism, Sepsis.

### Statistical Method

SPSS 13 software was used for analysis of the data obtained. The student's t test, fisher exact test and Karl Pearson correlation coefficient were used to test the significance between the study groups. Patients were grouped per the median value of NT-proBNP into the above median and below median cohorts, respectively.

### RESULTS

100 patients with STEMI who fulfilled all the inclusion criteria were enrolled in the study. The pertinent data both clinical as well as laboratory values were collected and then analysed accordingly. Majority of the cases were in the 61-70 Years age group adding to 33%, followed in descending order by the 51-60 Years group at 29%, then, the 41-50 Years group at 24%, then the more than 70 Years age group at 11% and finally the less than 40 Years group at 3%(Figure 1) and among them 72% were Male and 28% Females (Figure 2). Out of the cohort of 100 patients, by means of the ECG and the Echocardiography techniques 27% were diagnosed as Antero Lateral Wall MI, followed by, 27% Inferior Wall MI, 14% Anteroseptal MI, 12% Anterior Wall MI, and finally 10% Inferior Wall MI, Right Ventricular MI

(Figure 3). It was that 64% of the cohort has a history of smoking, followed by, 59% are Diabetics, 54% are Hypertensive, 27% are chronic consumers of alcohol, 26% possess a history of chewing tobacco, and 9% have a family history of IHD. (Figure 4). In the studied cohort 100% of the cases presented with chest pain, while 82% presented with sweating, 64% presented with breathlessness and only 22% presented with giddiness (Figure 5). Median Value of NT-proBNP was 1886 pg/ml and other statistics were as in Table 1.

Relation between NT-proBNP and smoking, alcohol consumption and tobacco chewing were as in Table 2, 3 and 4. Smoking had positive relation with NT-proBNP alcohol and tobacco chewing did not. Hypertension and Diabetes Mellitus

also did not show any relation with NT-proBNP (Tables 5 and 6). History of coronary artery disease in family had positive correlation with NT-proBNP (Table 7).

Presence of Breathlessness, considered as a symptom of Left Ventricular failure, had no relation to NT-proBNP level (Table 8). Correlation between NT-proBNP and LV Ejection fraction done by echocardiography was as in Table 9 and 10. 3% of the total patients had an Ejection Fraction of 20-25% and it is of note that the same patients also consistently had an NT-PRO BNP level of 3000pg/ml to be precise. It is also noted that in the entire cohort studied the largest percentage i.e. 36% presented with higher values of NT-PRO BNP (2501-3000Pg/ml). Of these 36% patients 52% had low ejection fractions i.e. 20%-30%. (Figure 6)

Name of Protocol	Minimum Value	Maximum Value	Mean	Median	Standard Deviation
NT-proBNP	358	3000	2049.93	1886	783.98
Age	38	78	58.3	60	9.66
Time of Presentation	1	9	4.68	5	2.18

**Table 1. NT-proBNP Statistics**

Smoking	NT-proBNP Levels		Sum
	<Median 1886 pg/ml	>Median 1886 pg/ml	
Absent	12	24	36
Present	37	27	64
Sum	49	51	100

**Table 2. NT-proBNP and Smoking**

Alcohol	NT-proBNP Levels		Sum
	<Median 1886 pg/ml	>Median 1886 pg/ml	
Absent	38	35	73
Present	11	16	27
Sum	49	51	100

**Table 3. NT-proBNP and Alcohol**

Chewing Tobacco	NT-proBNP Levels		Sum
	< Median 1886 pg/ml	>Median 1886 pg/ml	
Absent	32	42	73
Present	17	9	27
Sum	49	51	100

**Table 4. NT-proBNP and Chewing Tobacco**

Hypertension	NT-proBNP Levels		SUM
	< Median 1886 pg/ml	>Median 1886 pg/ml	
Absent	26	20	46
Present	23	31	54
Sum	49	51	100

**Table 5. NT-proBNP and Hypertension**

Diabetes Mellitus	NT-proBNP Levels		Sum
	<Median 1886 pg/ml	>Median 1886 pg/ml	
Absent	20	21	41
Present	29	30	59
Sum	49	51	100

**Table 6. NT-proBNP and Diabetes Mellitus**

Family History	NT-proBNP Levels		Sum
	< Median 1886 pg/ml	>Median 1886 pg/ml	
Absent	49	42	91
Present	0	9	9
Sum	49	51	100

**Table 7. NT-proBNP and Family History**

Breathlessness	NT-proBNP Levels		Sum
	< Median 1886 pg/ml	>Median 1886 pg/ml	
Absent	20	16	36
Present	29	35	64
Sum	49	51	100

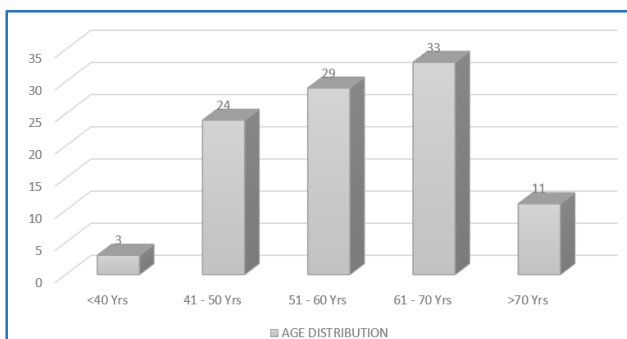
**Table 8. NT-proBNP and Breathlessness**

LVEF Values	NT-proBNP Levels					Total
	<1000	1001 – 1500	1501 – 2000	2001 – 2500	2501 - 3000	
20% - 25%	0	0	0	0	3	3
26% - 30%	0	0	1	4	16	21
31% - 35%	1	8	4	7	9	29
36% - 40%	5	19	14	1	8	47
<b>Total</b>	<b>6</b>	<b>27</b>	<b>19</b>	<b>12</b>	<b>36</b>	<b>100</b>

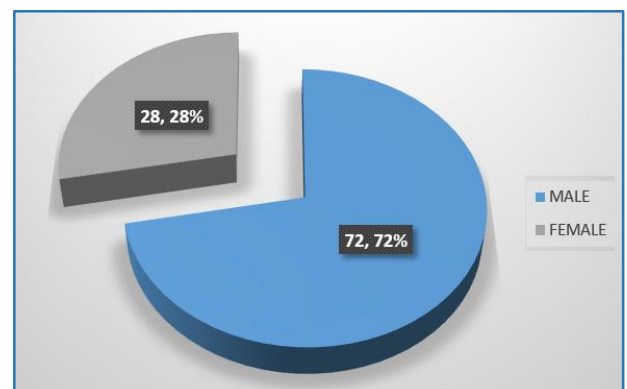
**Table 9. NT-proBNP and LV Ejection Fraction**

LV Ejection Fraction <40%	NT-proBNP Levels		Sum
	< Median 1886 pg/ml	>Median 1886 pg/ml	
<b>Absent</b>	17	8	25
<b>Present</b>	32	43	75
<b>Sum</b>	49	51	100

**Table 10. NT-proBNP and LV Ejection Fraction**



**Figure 1. Age Distribution**



**Figure 2. Sex Distribution**

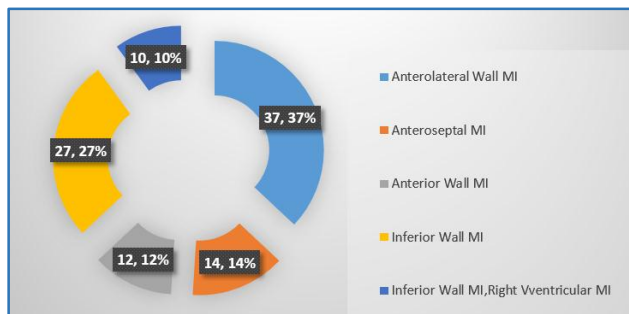


Figure 3. Diagnosis

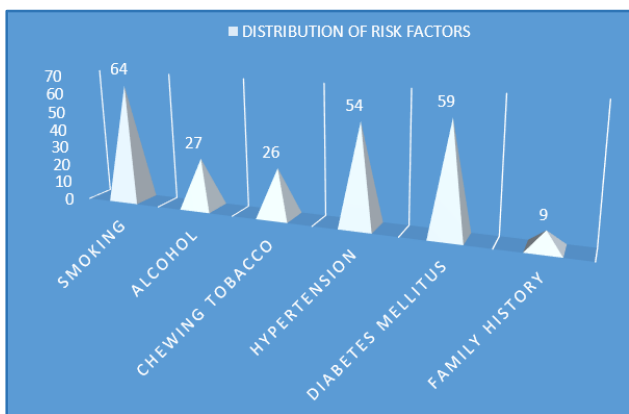


Figure 4. Distribution of Risk Factors

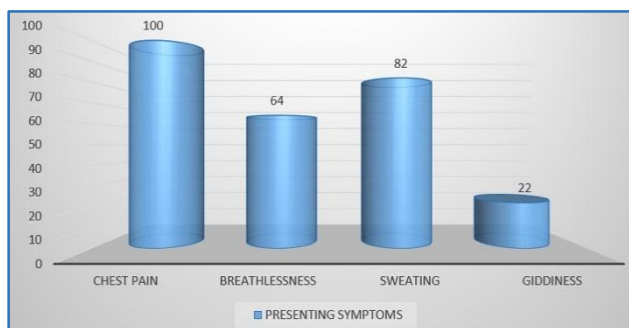


Figure 5. Presenting symptoms

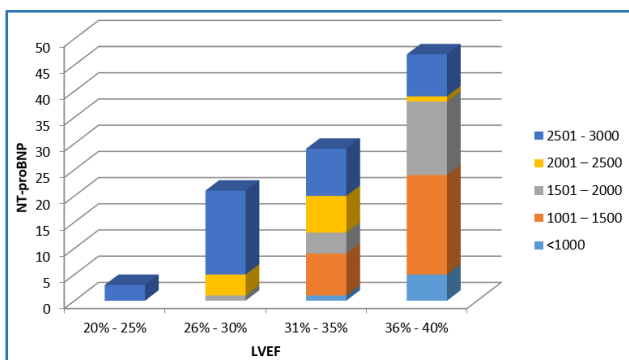


Figure 6. NT-proBNP and LV Ejection Fraction

**DISCUSSION**

BNP has been used to provide prognostic information in patients with acute coronary syndrome (ACS). Current knowledge indicates that NT-proBNP may be a more sensitive and an effective prognostic tool in these patients.<sup>1,2</sup>

In the present study, we have demonstrated that NTproBNP is a powerful predictor of adverse outcomes in

the patients presenting with STEMI while we were concentrating on the existence of systolic heart failure as our indicator.

NT-proBNP levels in our study varied per the infarct size and there was a wide scatter in the NT-proBNP levels presumably based on the extent of myocardial damage and functional impairment which directly correlates with adverse outcome under study. Similar scatter has been observed in other studies also.<sup>2</sup>

It is challenging to derive any prognostic cut-off value, implying that a single cut-off level cannot be used for NT-proBNP in the AMI population.<sup>1,2</sup> In clinical studies, natriuretic peptide concentrations have been reported as levels above or below the median value observed in the population under study, thus permitting a dichotomous approach to interpretation of the results.<sup>2,3,4,5</sup> In the present study, the mean NT-Pro BNP level was determined via statistical analysis to be 2049 pg/ml and the Median value was determined as 1886 pg/ml. In the full study cohort, NT-pro-BNP above median emerged as a good predictor of systolic heart failure with (p=0.03).

Many studies have proven the significance of NT-Pro BNP and its relation with systolic heart failure and the mechanism has been elucidated in detail in Part A of this study.

This study aimed to determine if the same levels can be used in acute phase as well during the initial presentation of the patient to the health care unit.

This has been proved beyond doubt by the statistical significance of the NT-Pro BNP levels and its relation with the echocardiographic ejection fraction values.

NT-proBNP measurement as a prognostic test has a distinct advantage over other currently available parameters since it is a quantitative test with precise values and is not operator-dependent, like the 2D Echo. The test doesn't have the drawbacks of inter and intra observer variability in quantifying the data obtained.

Our study, like many recent works, measured NT-proBNP instead of BNP due to its superior predictive value. Our results for NT-proBNP confirm and extend observations made regarding the value of NT-proBNP in patients with AMI.

Puri et al study had 80 STEMI patients. The mean levels of NT-proBNP were 2650±2760 pg/ml and the median was 1738 pg/ml. On univariate analysis and estimation of the -coefficient, NT-proBNP above median and EF <40% emerged as strong predictors of worsening heart failure, recurrent ischemia, repeat hospitalization and death at 30 days' post-event.

In a study by Galvani et al, patients with STEMI had median NT-proBNP of 201 ng/L (80 to 741 ng/L). Out of 1756 study subjects, 113 patients (6.4%) died within 30 days. 237 patients (13.5%) had recurrent ischemic events (51 subsequent MI, 213 recurrent angina), and 67 (3.8%) had severe heart failure.<sup>2</sup>

In a study by Vergé's et al NT-pro-BNP plasma levels were significantly higher in patients who died at hospital (800 (147 -3915) vs. 143 (55-357) pmol/L, p - 0.0001). NT-pro-BNP plasma levels were also significantly higher in

patients who suffered a cardiogenic shock during in-hospital stay compared with those who did not (680 (164–1577) vs. 137 (53–336) pmol/L,  $p=0.0001$ ). They found a strong association between the plasma NT-pro-BNP level and the level of risk for death or cardiogenic shock after MI.<sup>4</sup>

Ranjith et al in their study found that NT-proBNP levels were significantly increased in patients with STEMI ( $p=0.005$ ) and NSTEMI ( $p=0.002$ ) who developed adverse events during their hospital stay, compared with those who did not. NT-proBNP concentrations were superior to those of troponin T as prognostic markers in both STEMI and NSTEMI.<sup>6</sup>

In a study by Kwon et al patients with NT-proBNP > 991 pg/mL had lower LVEF ( $47.8 \pm 11.8\%$  vs.  $53.0 \pm 10.8\%$ ,  $p < 0.001$ ), needed longer intensive care ( $3.7 \pm 3.6$  days vs.  $2.8 \pm 2.4$  days,  $p < 0.001$ ) and had higher in-hospital mortality ( $1.3\%$  vs.  $7.4\%$ ,  $p < 0.001$ ) than those with NT-proBNP level  $\leq 991$  pg/mL.<sup>7</sup>

Ben-dor et al conducted a study on 55 STEMI patients and found that there was no significant correlation between NT-proBNP and systolic function early after STEMI ( $p=0.49$ ).<sup>8</sup>

Our study has contradicted the above findings by showing a correlation between the NT-Pro BNP values early post STEMI and the Systolic Function ( $p=0.03$ ).

In our study, the inclusion criteria were that the ejection fraction had to be less than or equal to 40%. Among them 51 patients (51%) had above median NT pro BNP values. There was no statistical significance in the relation between LVEF < 40% and the occurrence of complications, deaths. However, there was strong correlation between LVEF < 40% and NT-pro BNP above the median. ( $p = 0.030$ ).

In a study of 666 patients with acute MI, Richards et al found that LVEF was less, and left ventricular systolic and diastolic volumes significantly greater, in those incurring death, heart failure, or MI. Event rates in those with LVEF below 40% compared with above (or equal to) 40% were significantly higher for death, heart failure, and MI.<sup>9</sup>

Ranjith et al studied the role of Echocardiography and its comparison with NT-proBNP Measurements in 226 patients with acute MI. Using an EF  $\geq 50\%$ , 131 subjects (58%) were found to have preserved L V systolic function with no evidence of diastolic abnormalities. Only 3 % had severe LV dysfunction. No significant differences were found between the occurrence of the complications and deteriorating LV contractile function on echocardiography.<sup>10</sup>

## CONCLUSIONS

- NT-PRO BNP is a good predictor of heart failure in settings of acute mi.
- NT-PRO BNP is a good tool for risk stratification of acute mi patients so that appropriate treatment can be planned.

- NT-PRO BNP can be used in an acute setting as well and can accurately predict heart failure in the absence of echocardiography, hence can be used in remote areas as a good tool.

## REFERENCES

- [1] Chan D, Ng LL. Biomarkers in acute myocardial infarction. *BMC Med* 2010;8:34.
- [2] Galvani M, Ottani F, Oltrona L, et al. N-Terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. *Circulation* 2004;110(2):128-134.
- [3] Mega JL, Morrow DA, De Lemos JA, et al. B-type natriuretic peptide at presentation and prognosis in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004;44(2):335-339.
- [4] Verge's B, Zeller M, Desgre's J, et al. High plasma N-terminal pro-brain natriuretic peptide level found in diabetic patients after myocardial infarction is associated with an increased risk of in-hospital mortality and cardiogenic shock. *Eur Heart J* 2005;26(17):1734-1741.
- [5] Talwar S, Squire IB, Downie PF, et al. Profile of plasma N-terminal proBNP following acute myocardial infarction; correlation with left ventricular systolic dysfunction. *Eur Heart J* 2000;21(18):1514-1521.
- [6] Ranjith N, Pegoraro RJ, Naidoo DP, et al. Prognostic value of N-terminal-pro-brain natriuretic peptide measurements in patients with acute coronary syndromes. *Cardiovasc J S Afr* 2006;17(2):60-66.
- [7] Kwon TG, Bae JH, Jeong MH, et al. N-terminal pro-B-type natriuretic peptide is associated with adverse short-term clinical outcomes in patients with acute ST-elevation myocardial infarction underwent primary percutaneous coronary intervention. *Inter J Cardiol* 2009;133(2):173-178.
- [8] Ben-Dor I, Haim M, Rechavia E, et al. Serum NT-proBNP concentrations in the early phase do not predict the severity of systolic or diastolic left ventricular dysfunction among patients with ST-elevation acute myocardial infarction. *Angiology* 2007;57(6):686-693.
- [9] Richards AM, Nicholls MG, Espiner EA, et al. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation* 2003;107(22):2786-2792.
- [10] Ranjith N, Pegoraro RJ, Naidoo DP, et al. The role of echocardiography and its comparison with NT-proBNP measurements in patients with acute myocardial infarction. *Med Sci Monit* 2007;13(12):CR574-578.