



The Relationship between Serum NT-Pro-BNP Levels and Prognosis in Patients with Systolic Heart Failure

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ABSTRACT

Introduction: Most studies reported using N-terminal pro-brain natriuretic peptide (NT-proBNP) in diagnosis of heart failure but there is controversy about use of these tests in determining prognosis and classification of severity of heart failure. The objective of this study was to determine the value of plasma NT-proBNP levels assessment in evaluation of mortality and morbidity of patients with systolic left ventricular dysfunction. **Methods:** A cohort study was performed in 150 patients with heart failure since September 2009 until February 2010. The patients were followed for 6 months to assess their prognosis. Patients were divided into two good and bad prognosis groups according to severity of heart failure in New York Heart Association (NYHA) class and frequency of hospital admission and mortality due to cardiac causes. Patients with good prognosis had ≥ 1 admission or no mortality or NYHA class ≥ 2 and patients that had one of this criteria considered as bad prognosis groups. Pro-BNP levels were measured at baseline and left ventricular ejection fraction (LVEF) was estimated with echocardiography. Data was analyzed with using Chi-square, t-test, ANOVA, Kruskal-Wallis tests. **Results:** In patients with heart failure that enrolled in this clinical study, ten patients were lost during follow-up. The mean of NT-proBNP is significantly correlated with ejection fraction ($p=0.003$) and NYHA class ($p<0.001$). In our study among 140 patients who were follow-up for 6 months, 11(9.7%) of individuals died with mean NT-proBNP of 8994.8 ± 8375 pg/ml, in survived patients mean NT-proBNP was 3756.8 ± 5645.6 pg/ml that was statistically significant ($P=0.02$). Mean NT-proBNP in the group with good prognosis was 2723.8 ± 4845.2 pg/ml and in the group with bad prognosis was 5420.3 ± 6681 pg/ml, difference was statistically significant ($P=0.0001$). **Conclusion:** Our study in consistent with other studies confirms that NT-proBNP is significantly correlated with mortality and morbidity. This could be predicting adverse out come and stratification in patients with heart failure. It is recommended that more research be performed in Iran.

Introduction

Heart failure (HF) is a major public health problem in industrialized nations and the United States is responsible for approximately one million cases and 50,000 hospital deaths annually.¹

Heart failure has cost in the USA over 8 million dollars a year and 5% of all admissions in the UK

(United Kingdom) are diagnosed with heart failure.² The prevalence of heart failure is increasing in many parts of the world and prognosis is poor, especially if the symptoms are due to left ventricular systolic dysfunction (LVSD). If patients are treated with Renin-Angiotensin blockers system, Aldosterone blockers, and B-blockers properly, prognosis could be better. Thus the main

importance is to identify LVSD fast in patients to start appropriate treatment with the confidence. Repeatedly shown that the diagnosis of heart failure in suspected patients are not reliable; patients with suspected heart failure should be sent for echocardiography commonly, but in many countries echocardiography is hardly possible due to limited services in primary care. Records obtained more than 10 years ago shows that natriuretic peptides are markers of left ventricular wall stress, especially brain natriuretic peptide (BNP) or N-terminal product derived (NT-proBNP) peptide progenitor, that possible resolve this problem.

Many studies have investigated the effect of natriuretic as a diagnostic factor of left ventricular dysfunction in patients.³ BNP is secreted by myocardial cells in response to increased volume and pressure. This precursor molecule is divided into active BNP and inactive N-Terminal fragment Pro-BNP (NT-Pro-BNP). Comparison of BNP and NT-Pro-BNP has shown that both molecules effective in diagnosing left ventricular dysfunction in acute care and rapid decision. All studies have shown NT-Pro-BNP levels as predictors of future cardiovascular changes and mortality following acute coronary syndromes.⁴ In an article published in 2005 it has reported that the in patients have been sent for echocardiography with suspected heart failure in primary care, NT-Pro-BNP levels are effective in refuse of left ventricular failure.³ Most studies are using Pro-BNP in diagnosis of heart failure but use of these tests in determining prognosis and classification of severity of heart failure is controversy. So, in this study we tried to determine the severity of heart failure according to Pro-BNP measurement that offer lower cost and faster method for assess the patients in emergency and classification of heart failure and thus reduce follow up costs and unnecessary admissions.

Materials and methods

In this cohort study 150 patients with heart failure, that were admitted to Zanjan, Vali-asr and Beheshti hospitals and emergency rooms since September 2009 until February 2010 have been included. In patients with heart failure, severity were divided into four classes (I, II, III, IV) based on New York Heart Association functional classification (NYHA). Class I (mild), no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath). Class II (mild), slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea. Class III (moderate), marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class IV (severe), unable to carry out any physical activity without discomfort. If any physical activity is undertaken, discomfort is increased.

All data were collected in questioners by a general physician. Patients with hyperthyroidism, acute pulmonary embolism, COPD, sepsis excluded from study. Ejection fraction (EF) determined with echocardiography by HDI 3500 was recorded in the initial questionnaire. Then 2 ml of blood was drawn after fasting for at least 8 hours and 20 minutes rest on arrival at the laboratory and after separation serums were kept at -70°C .

At the storage conditions, Pro-BNP serum levels will be sustained for at least 12 months. Pro-BNP were measured using ECLIA (electrochemiluminescence immunoassay), Roche company Germany and apparatus (Roche Co., Germany) Elecsys 2010. Mean while inter assay precision and total precision is reported for this method less than 7.2 and 2.3 percent respectively. Analytical sensitivity and functional sensitivity for ECLIA are 5 pg/ml and 50 pg/ml respectively. Patients were follow-up from the time of Pro-BNP serum measurement until 6 months for prognosis status (changing of the severity of heart failure and frequency of hospital admission and mortality due to cardiac causes) and this information was recorded in the period questionnaires that were completed in two months intervals. Patients were divided to two good and bad prognosis groups. Patients with good prognosis had ≥ 1 admission or no mortality or NYHA class ≥ 2 and patients that had one of this criteria considered as bad prognosis groups. Data were analyzed using frequency distribution, indices and central distribution and Chi squared, ANOVA, Kruskal Wallis, t-test and Risk Calculation by SPSS 14.

Results

In this study we studied 150 patients, 90 males (60%) and 60 females (40%). Patients had minimum age of 23 years old and maximum age of 102 years old, mean age was 58.7 ± 13.0 years old. In this study, 87 patients had only coronary artery disease. The mean Pro-BNP in patients was 4472.0 ± 6554.6 pg/ml and the highest level was 35000 and lowest level was 43.96 pg/ml. With increasing in heart failure functional class, mean Pro-BNP levels also increase which is statistically significant, (ANOVA, $P=0.02$; kruskal Wallis, $P=0.0001$; Table 1).

Table 1. Mean Pro-BNP levels according to heart failure classification

Heart failure class	N (%)	Mean ± SD (pg/ml)
I	38(25.3)	2100.3±2967.5
II	52(34.7)	4099.4±42 33.3
III	34(22.7)	6263.9±8071.6
IV	26(17. 3)	6340.5±10180.0

In this study, 10 patients were excluded from the study due to lack of access or change of place of residence. Among the 140 people, 38 patients had one admission during this period, 17 patients had two admissions and 11 patients had three times or more admission and 74 patients had not hospital admission at all time. Mean Pro-BNP increased with increasing the number of hospital admission (ANOVA, P = 0.25; kruskal Wallis, P=0.01; Table 2).

Table 2. Relationship between Pro-BNP levels and hospital admission

Number of admission	N (%)	Mean ± SD (pg/ml)
0	74 (52.9)	3377.6±5635. 2
1	38 (27.1)	4683.0±5581. 4
2	17 (12.1)	6498±8123. 8
≥3	11 (9.7)	4109.6±6196. 0

There was no significant difference in mean Pro-BNP level between male and female, (4314.6 ± 5824.1 vs. 4576±7029.3), (t-test, P=0.81; Mann-Whitney U, P =0.95). Pro-BNP levels in our study were investigated at different ages that mean Pro-BNP increased with age but this difference was not significant statistically, (Kruskal Wallis, P=0.15; ANOVA, P=0.07).

Pro-BNP levels according to the underlying disease of patients are given in Table 3. The mean Pro-BNP levels in patients who had combination of hypertension (HTN) and coronary artery disease (CAD) as underling disorders of heart failure were higher than those who had only HTN or CAD, (kruskal wallis ,P=0.16; ANOVA, P=0.57).

Table 3. Relationship between Pro-BNP levels and underlying disease

Diseases	N	Mean ± SD (pg/ml)
CAD	87	4125.0±5997.5
HTN	18	3652.9±7109.6
CAD&HTN	31	5907.0±8688.9
Others	14	4504. 2±2736.8

CAD: Coronary Artery Disease, HTN: Hypertension, Others: Cardiomyopathy, Diabetes, Valvular heart disease

Patients were divided based on cardiac ejection fraction (EF). Mean Pro-BNP levels increased with increasing of heart failure class that was significant statistically, (ANOVA, P=0. 02; kruskal Wallis, P =0.003; Table 4).

Table 4. Relationship between Pro-BNP levels and EF

EF	N	Mean ± SD (pg/ml)
19-10	12	8399.2±8747.5
29-20	84	4885.2±7199.4
≥30	54	2956.6±4198.6

In our study among 140 patients with heart failure who were followed for 6 months, 11(9.7%) died and mean Pro-BNP was 8994.8±8375 pg/ml in these patients and in other patients who survived during 6 months, was 3756.8±5645.6 pg/ml which showed the difference was significant statistically, (Mann-Whitney U, P=0.02). Mean Pro-BNP was 5054.8 pg/ml among those admitted while in people who was not, mean Pro-BNP was 3377.6 pg/ml that difference was statistically significant (P=0.002). The mean age of heart failure patients who died was 74.8 years and in living people 67.5 years, this difference was statistically significant, (P=0.08, t-test) and (P=0.06, Mann-Whitney U test).

The mean age among those patients who admitted (66 patients) was 70.4 years and in non-admitted patients (74 cases) was 66.1 years that was statistically significant, (P =0.05, t-test). Patients were divided based on prognosis, to two groups with good (n=65) and bad (n=75) prognosis. Patients with good prognosis had higher ejection fraction. Mean age of patients with good prognosis were 65.6±4.5 years and bad prognosis group were 70.3±10.6 years and this difference was statistically significant, (t-test, P = 0.03; Mann-Whitney U; P=0.06). Mean Pro-BNP in the patient with good prognosis was 2723.8± 4845.2 pg/ml and in the patient with bad prognosis was 5420.3±6681 pg/ml, that this difference was statistically significant t-test, P = 0.007; Mann-Whitney U, P = 0.0001).

Discussion

The main finding of this study was that during 6 month follow-up of patients with heart failure, whatever the class of heart failure increases, the average Pro-BNP levels also increased. The plasma level of Pro-BNP, which is secreted mainly from the ventricle, is a well-established powerful risk marker in HF.

Several authors have reported that plasma Pro-BNP is a prognostic predictor of mortality and morbidity in patients with HF.⁵⁻⁸ In this study, the mean level Pro-BNP was determined based on the underlying disease and patients with concurrent CAD and HTN showed the highest level of Pro-BNP. Also our study showed that the mean Pro-BNP was high among the elderly. In our study, the mean level of Pro-BNP increased statistically significant with the severity of heart failure based on NYHA classification, similar to most of studies, especially in China⁹ and Italy¹⁰. In this study, the mean Pro-BNP levels showed an increase with increasing frequency in hospitalized patients with heart failure, according similar to studies in Denmark.^{11,12}

In our study, mortality was lower in patients with low Pro-BNP levels in agreement with study in Denmark that showed³ low levels of Pro-BNP is associated with lower risk of death, independent of age, sex and left ventricular EF. The mortality rate in patients with high amounts of Pro-BNP were higher according to another study in Britain and Germany¹³ that high values of mean Pro-BNP is listed as an independent predictor for mortality, and other studies¹⁴⁻¹⁶ refers to it.

Our study showed that in patients who severity of heart failure according to NYHA classification was increased, had high mean Pro-BNP and their prognosis was bad that consistent with Masson *et al.* study in Italy¹⁷. In this research, patients with high Pro-BNP had a bad prognosis than patients with lower Pro-BNP agreement with Lim *et al.* study in England.⁷ In our study, patients with low mean Pro-BNP similar with Dunn *et al.* study were not admitted during the six-month follow-up¹⁸ that could be helpful in identifying outpatient to determine the risk of hospitalization in heart clinic. Patients with concurrent CAD and HTN had higher amounts of Pro-BNP in our study which none of other studies have not mentioned. In our study, mortality was 11 (7.9%) among 140 patients with heart failure during 6 months follow-up and mean Pro-BNP in these patients showed significant difference with patients who were alive at the end of six months. Mortality rate was 9 patients (10.1%) in De Bernardi *et al.* research in Italy¹⁹ during one-year follow-up in 89 patients and mean Pro-BNP was 1864.0 pg/ml that was consistent with our study. In Amir *et al.* study²⁰ mortality rate was 26% and mean Pro-BNP was 1958 pg/ml. High mean Pro-BNP is strongly associated

with severity heart failure in Iranian population. Mean Pro-BNP in our study was 4472 pg/ml and in De Bernardi *et al.* study mean Pro-BNP was 1370 pg/ml.²¹ In our study, the mean age of heart failure patients who died was 74.8 years and mean Pro-BNP was 8994 pg/ml. In Hunt *et al.* study²² in patients 75 years and more mean Pro-BNP was higher than 3855 pg/ml. Probably high mean Pro-BNP among our patients is due to severity of disease.

In Tsutamoto *et al.* study in Denmark⁵ low amounts of Pro-BNP roll out the left ventricular systolic dysfunction. Daniela study in Italy¹⁰ was shown significant relationship between NT-Pro-BNP and ejection fraction. Finally NT-Pro-BNP and abnormal echocardiography provide independent information for predicting prognosis in patients with heart failure that consistent with Lim *et al.* study.⁷

Conclusion

The major limitation in this study was that we did not find similar study in Iran that comparison Pro-BNP levels in Iranian healthy with heart failure patients. However we concluded that the measurement of Pro-BNP levels in heart failure patients could be used as an economic marker for evaluation of mortality and morbidity.

Ethical issues: The study was approved by the Ethical Committee of the University.

Conflict of interests: No conflict of interest to be declared.

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