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# Prognostic value of N-terminal pro-B-type natriuretic peptide in patients with severe acute decompensated heart failure

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**SUMMARY**
*Objective:* A prospective study was performed to determine the relation between plasma N-terminal pro brain natriuretic peptide (NT-proBNP) levels and short- and long-term mortality in patients with acute heart failure (AHF).
*Settings:* 1st Department of Medicine, Institute of Clinical Biochemistry and Diagnostics, Institute of Clinical Immunology and Allergology, Charles University Prague, Medical Faculty and Faculty Hospital Hradec Králové.
*Methods:* NT-proBNP levels were measured at time of admission in 92 consecutive patients with AHF.
*Results:* During one-year follow-up, 32 patients died. Mean levels of NT-proBNP were significantly lower among the survivors (NT-proBNP: 7 855.4 ± 9 919.9 ng/l, vs.15 470.6 ± 11 273.1, $p < 0.001$). Hazard ratio (HR) for death from any cause for the patients with NT-proBNP levels above median as compared with those with NT-proBNP below median was 2.91 (0.84–10.10) for 7-day, 3.58 (1.17–11.1) for 28-day, and 3.76 (1.49–9.55)*:* for 1-year mortality.
*Conclusions:* NT-proBNP levels are elevated in acute heart failure, NT-proBNP is also the marker of short- and long-term mortality in acute decompensated heart failure patients, and provides prognostic information above and beyond that provided by conventional cardiovascular risk factors.
*Key words:* acute heart failure, mortality, natriuretic peptides, mortality.

**SOUHRN**
**Pudil R., Tichý M., Andrýs C., Bláha V., Vojáček J.: Prognostický význam NT-proBNP u pacientů s těžkým akutním dekompenzovaným selháním srdce**
*Cíl studie:* Posoudit vztah mezi plazmatickou hladinou N-terminálního mozkového natriuretického peptidu (NT-proBNP) a parametry krátko- i dlouhodobé mortality pacientů s akutním srdečním selháním.
*Název a sídlo pracoviště:* 1. interní klinika, Ústav klinické biochemie a diagnostiky, Ústav imunologie a alergologie, Lékařská fakulta Univerzity Karlovy a Fakultní nemocnice, Hradec Králové.
*Materiál a metody:* V souboru 92 pacientů s akutním srdečním selháním byla změřena hladina NT-proBNP ze vzorku krve odebraného v době přijetí. Parametry krátko- i dlouhodobé mortality byly stanoveny z dat z následného jednoročního sledování vyšetřovaného souboru.
*Výsledky:* V průběhu sledování klinického stavu do konce prvního roku 32 pacientů zemřelo. Průměrná hladina NT-proBNP byla u přeživších pacientů významně nižší (NT-proBNP: 7 855,4 ± 9 919,9 ng/l, vs 15 470,6 ± 11 273,1, $p < 0,001$). Hazard ratio (HR) pro úmrtí z jakékoliv příčiny u pacientů nad medián bylo 2,91 (0,84–10,10) pro 7denní, 3,58 (1,17–11,1) pro 28denní a 3,76 (1,49–9,55) pro jednoroční mortalitu.
*Závěr:* Hladina NT-proBNP je významně zvýšena u pacientů s akutním srdečním selháním. Analýza ukázala, že hladiny NT-proBNP jsou u pacientů s akutním srdečním selháním ukazatelem krátko- i dlouhodobé mortality.
*Klíčová slova:* akutní srdeční selhání, natriuretické peptidy, mortalita.

## 1. Introduction

Synthesis of natriuretic peptides and immune activation represents an important part of neurohumoral response to heart failure. Brain type natriuretic peptide is released primarily from the ventricles in response to myocyte stretch [1]. It is synthesized as an inactive prohormone that is split into active hormone BNP and the inactive N-terminal fragment (NT-proBNP). BNP has a number of systemic effects, including vasodilation, increased sodium excretion and urinary volume, inhibition of the renin-angiotensin-aldosteron system and sympathetic nervous system [2, 3]. The main pathological process resulting in increased synthesis and release of BNP and NT-proBNP is impairment of left ventricular systolic or diastolic function [4–6]. It was demonstrated that the assessment of natriuretic peptides (BNP and NT-proBNP) has pathophysiological and clinical importance for clinical evaluation and risk stratification of the patients with heart failure [7, 8]. High levels of natriuretic peptides identify those at greatest risk of future serious cardiovascular events including death [9–11]. There is also recent evidence that adjusting heart failure therapy in order to reduce natriuretic peptides levels in individual patients may improve outcome [12, 13]. In addition, BNP is an important prognostic marker in patients with heart failure [14–17].

The aim of this study is to evaluate the association between NT-proBNPlevel on 7-day, 28-day and 1-year all causes mortality in patients with acute heart failure.

## 2. Materials and methods

### 2.1. Study design and patients

*Patients*

A group of 92 consecutive patients aged 22 to 85 years (62.28 ± 13.96 yrs, 65 men) with acute heart failure were enrolled into a prospective observational study of the prognostic value of NT-proBNP. Inclusion criteria were hospitalization for acute heart failure (*de novo* or as decompensation of chronic heart failure). Patients presenting acute myocardial infarction (ESC/ACC criteria for the diagnosis of AMI were used), and sepsis, serious lung disease, cancer, renal failure, and volume overload caused by serious renal and liver disease were excluded.

*Control group*

Healthy individuals [mean (SD) age 46.74 (16.75) years, 13 women and 13 men] nonobese, normotensive, and free from acute diseases, and they all denied the use of any medication during the 4 weeks before the study. They all had normal plasma values for main plasma indices and non-pathologic erythrocyte and leukocyte counts and normal urine analysis. In all of the participants, a complete cardiologic examination, including electrocardiogram and echocardiographic investigation (left ventricular ejection fraction > 55%), was performed. In the subjects > 50 years of age, an effort stress test (bicycle ergometry) was performed to exclude asymptomatic heart disease. Cardiac morphology and function were assessed by echocardiography.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by The Ethical Committee of our institution. The data on history, physical examination, echocardiography, laboratory findings and 28-day follow-up period were prospectively collected for all patients. One-year mortality data were obtained from a registry of our hospital and from physicians of the patients.

### 2. 2. Blood sampling and laboratory analysis

Blood samples for the measurement of NT-proBNP were obtained by venipuncture at the time of admission. Blood samples were collected into chilled tubes containing EDTA, immediately placed on ice, promptly centrifuged (2700 g at 4 °C for 10 minutes), and then plasma was decanted and stored in -20 °C until assayed. NT-proBNP was measured with use of the commercially available immunoassay based on sandwich technique (Elecsys pro BNP, Roche Diagnostics). The analytical range extends from 20 to 35 000 ng/l.

### 2. 3. Assessment of cardiovascular functional parameters

Killip classification was used to assess clinical severity of acute heart failure. Within 12 hours from the admission, all patients underwent echocardiographic examination with assessment of left ventricular ejection fraction (LVEF) using the Simpson's method [18, 19].

### 2. 4. Statistical analysis

Data are presented as mean ± SD or as median (interquartile range), as appropriate. NT-proBNP data were log transformed. Baseline characteristics were compared among the survivors and non-survivors with the use of Student's test or $\chi^2$ as appropriate. Survival curves were generated by means of Kaplan-Meier estimates. To evaluate mortality data, relative risks and 95 percent confidence intervals were calculated as hazard ratios derived from the Cox regression model. Multiple regression analysis was fitted with the use the clinical covariates.

## 3. Results

### 3. 1. Clinical characteristics of study population

Demographic, clinical and laboratory data of control group and study population at the time of admission are presented in Table 1. One year follow-up of the patients was complete. Medication after hospital discharge included: diuretics 78 pts (100%), beta--blockers 65 (83%), ACE inhibitors (AT II blockers) 72 (92%), acetylsalicylic acid 58 (74%). The plasma level of NT-proBNP was significantly elevated in all patients. Presence of chronic coronary artery disease was the most frequent cause of heart failure. One third of patients had arterial hypertension. Diabetes was present as a risk factor in almost 45% of patients, and 37 percent of patients were smokers. Of the 92 patients, 56 (61%) had previous history of heart failure, but this fact had no significant impact on plasma NT-proBNP level. The mean plasma creatinine level was 117.4 ± 24.2 μmol/l, mean total cholesterol level was 5.9 ± 1.2 mmol/l. In multiple regression analysis, plasma NT-proBNP level was closely associated only with plasma creatinine level ($p < 0.01$), left ventricular ejection fraction ($p < 0.01$), and independent on risk factors as age, gender, previous history of coronary artery disease or previous history of heart failure, diabetes mellitus, smoking and hyperlipidemia. Basic haemodynamic data were as follows: mean systolic/diastolic blood pressure was 140.3 ± 23.1/83.6 ± 12.4 mmHg, mean heart rate was 96.5 ± 22.4 bpm. 26 (28.2%) patients had left ventricular hypertrophy (left ventricular mass index > 134g/m$^2$ body surface area for men or > 110 g/m$^2$ in woman, (calculation according to Devereux formula).

### 3. 2. Analysis of mortality

During one-year follow-up, 32 patients (34.8%) died. Among the baseline characteristics associated with 1-year mortality were: plasma NT-proBNP level and Killip class 3 and 4. One-year mortality was not associated with age, gender, presence of diabetes mellitus, systemic hypertension, atrial fibrillation, history of coronary artery disease and smoking status (Table 2).

**Table 1.** Clinical characteristics of study population

| | Control group (n = 26) | Patient group (n = 92) | *p* |
|---|---|---|---|
| Age, y ± SD | 46.74 ± 16.75 | 62.28 ± 13.96 | < 0.05 |
| LVEF (%) | 63.65 ± 5.06 | 34.16 ± 14.27 | < 0.001 |
| Female gender, n (%) | 13 (50) | 27 (29.3) | ns |
| CAD, n (%) | 0 | 75 (81.5) | |
| DCM, n (%) | 0 | 11 (11.9) | |
| Prior history of HF, n (%) | 0 | 56 (61) | |
| Valvular disease, n (%) | 0 | 6 (6.5) | |
| Systemic hypertension, n (%) | 0 | 31 (33.69) | |
| Diabetes, n (%) | 0 | 41 (44.56) | |
| Smoking, n (%) | 0 | 34 (36.9) | |
| Atrial fibrillation, n (%) | 0 | 26 (28.26) | |
| NT-proBNP [ng/l] | 78 (54–110) | 6 277 (2 639–11 562) | < 0.0001 |

LVEF = left ventricular ejection fraction, CAD = coronary artery disease, DCM = dilated cardiomyopathy, HF = heart failure

**Table 2.** Baseline characteristics associated with one-year mortality

| Variable | Survivors (n = 60) | Deceased (n = 32) | *p* |
|---|---|---|---|
| Age, y ± SD | 65 ± 16 | 68.5 ± 6.4 | ns |
| Female, n (%) | 18 (30) | 9 (29) | ns |
| Diabetes mellitus, n (%) | 27 (45) | 14 (43) | ns |
| Systemic hypertension, n (%) | 19 (32) | 12 (37) | ns |
| Smoking, n (%) | 25 (42) | 9 (28) | ns |
| History of CAD, n (%) | 50 (80) | 25 (78) | ns |
| Prior history of HF, n (%) | 35 (58) | 21 (65) | ns |
| Atrial fibrillation, n (%) | 18 (30) | 8 (25) | ns |
| Plasma NT-proBNP [ng/l] | 3 811 (2 566–6 377) | 10 985 (8 861–19 846) | 0.001 |
| LVEF % | 35 ± 14 | 31.8 ± 12.9 | ns |
| Killip class > 2 | 4 | 15 | 0.001 |

There was increased mortality among the patients with increasing quartiles of NT-proBNP (Fig. 1). The Kaplan-Meier survival curves for the quartiles diverged early and continued to separate by the end of 365-day period. At one-year follow-up, the difference in mortality between the quartiles was statistically significant $p < 0.001$, with a mortality of 0% (0), 9% (8), 12% (11), and 14% (13). In a multivariable logistic regression analysis after adjusting for predictors, plasma NT-proBNP levels and Killip class 4 still independently contributed to the prediction of 7-day, 28-day and 1-year mortality in patients with acute heart failure.

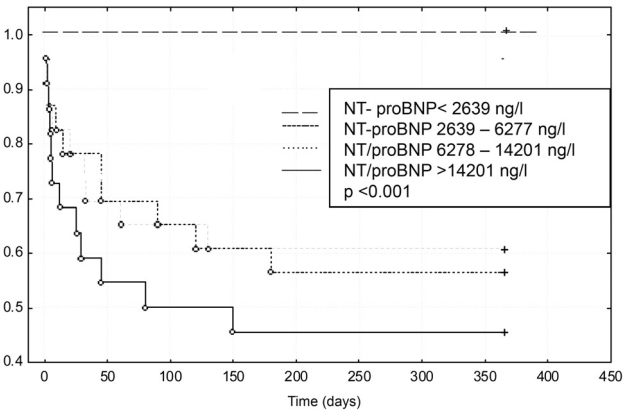


**Fig. 1.** Kaplan-Meier survival curves of patients with acute heart failure according to quartiles of plasma NT-proBNP

## 4. Discussion

The increase of plasma natriuretic peptide levels in patients with heart failure has been studied previously. The increase of the brain natriuretic peptide synthesis in heart failure is caused by volume and pressure overload of myocytes [1]. The plasma natriuretic peptide levels can be influenced not only by heart failure, but also by other factors (age, gender, presence of arterial hypertension and renal functions) [11]. It has been shown that the increase of NT-proBNP caused by these factors plays only additional role to increase caused by acute decompensation of heart failure. Furthermore, it has been shown, that plasma natriuretic peptide level can correlate with heart failure severity in patients with acute and chronic heart failure [4, 6, 16]. In the previous study, we found good correlation between echocardiographic parameters and plasma NT-proBNP levels [20]. We found statistically significant correlation of vena cava inferior diameter and plasma NT-proBNP level [21]. Also other studies showed the association of heart failure severity and plasma BNP/NT-proBNP levels [22]. It has been already shown, that normal levels of natriuretic peptides have strong negative predictive value for the presence of left ventricular failure. Therefore, the assessment of natriuretic peptides has been implemented into the guidelines for diagnosis and treatment of acute heart failure.

The progostic role of NT-proBNP has been also studied. Januzzi et al. [17, 23] have conducted study of plasma NT-proBNP and its role in diagnosis, treatment and prognosis of patients with acute dyspnea. They confirmed significant role of natriuretic peptides not only in diagnosis, but also in prognosis of the patients with heart failure.

In the present study, we found that patients with acute decompensated heart failure (ADHF) had significantly elevated plasma level of NT-proBNP. Furthermore, in our study we found that NT-proBNP measured immediately after the admission to hospital in patients with ADHF provides independent prognostic information on all causes mortality.

In summary, this study demonstrates that plasma NT-proBNP level is increased in acute heart failure

and can serve as a strong predictor of 7-day, 28-day and one-year mortality. Therefore, plasma NT-proBNP level can also as a useful tool in risk stratification of these patients.

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