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Lack of decrease in plasma N-terminal pro-brain natriuretic peptide identifies acute heart failure patients with very poor outcome

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Abstract

Background: Optimal risk stratification in heart failure patients surviving an episode of acute decompensation has not yet been established. We investigated whether a lack of significant decrease in plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) during hospital stay can identify patients at high risk of poor outcome.

Methods: We studied 103 consecutive patients with acute heart failure (86 men, age: 64±13 years, LVEF: 28±8%). The primary end-point was all-cause mortality at 1-year follow-up.

Results: Median plasma NT-proBNP on admission was 6116 pg/mL (upper/lower quartiles: 3575, 10,958) vs. 2930 pg/mL (1674, 5794) after clinical stabilization (7±3 days after admission). During the 1-year follow-up 29 (28%) patients died. A decrease in plasma NT-proBNP during clinical recovery (expressed as percentage of NT-proBNP on admission) predicted favorable outcome in the single predictor analysis ($p<0.001$) and multivariable analyses ($p<0.001$). Receiver operating characteristic curve analysis revealed that 65% was the cut-off value for NT-proBNP decrease having best prognostic accuracy for predicting death (sensitivity 90%, specificity 37%, AUC=0.65, 95% CI: 0.54–0.74). Kaplan–Meier analysis showed that 12-month survival was 92% (95% CI: 81–100%) for patients with ≥65% NT-proBNP decrease vs 66% (95% CI: 56–76%) in those with <65% NT-proBNP decrease ($p=0.02$).

Conclusions: The magnitude of plasma NT-proBNP decrease in patients with acute heart failure is helpful in discrimination of patients at high risk of death. Plasma NT-proBNP level monitoring is important for risk stratification in this group of patients.

Keywords: Decompensated heart failure; N-terminal pro-brain natriuretic peptide; Prognosis

1. Introduction

Patients with heart failure (HF) who develop an episode of acute decompensation have high mortality and morbidity [1–4]. Optimal risk stratification in this population remains difficult, because traditional prognosticators with an established role in chronic HF may not be simply applicable [1–5].

Circulating levels of brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) have been documented to be useful for diagnosis of HF and also for clinical monitoring and risk stratification across the whole spectrum of the disease [6–12]. An episode of acute heart failure (AHF), characterized by hemodynamic deterioration and related neuroendocrine activation, results in an excessive production of BNP [13,14]. Therapy directed towards hemodynamic stabilization and left ventricle unloading may significantly decrease circulating levels of natriuretic peptides [12,15,16]. Until now, only few studies have examined usefulness of serial evaluation of BNP/NT-proBNP during hospital stay in patients with AHF for monitoring of response to therapy and prognostic assessment [17–20].

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Thus, we performed the prospective study in order to establish whether in these patients a lack of significant decrease in plasma levels of NT-proBNP during hospital stay can identify those at high risk of poor outcome during 1-year follow-up.

2. Methods

2.1. Study population

We prospectively evaluated patients admitted to our Cardiology Department who met the following inclusion criteria: (1) diagnosis of AHF based on the European Society of Cardiology criteria [21], and (2) left ventricular ejection fraction (LVEF) <45% as assessed by echocardiography on admission. Exclusion criteria included: (1) acute coronary syndrome as a primary cause of AHF; (2) AHF due to drug induced hypotension; (3) coronary revascularisation within 3 months preceding the study; (4) death during hospitalization; (5) history of malignant disease, and (6) lack of patient's consent.

AHF was classified according to the European Society of Cardiology guidelines [21], as: (1) hypertensive HF, (2) pulmonary edema, (3) cardiogenic shock, (4) high output failure, (5) right HF, or in the cases not fulfilling [1–5] criteria as (6) acute decompensated HF.

The study protocol was approved by the local ethics committee, and all subjects gave written informed consent. The study was conducted in accordance with the Helsinki Declaration.

2.2. Laboratory measurements

On hospital admission each patient underwent a physical examination. Routine laboratory tests were performed by standard techniques in our laboratory, of which hemoglobin, creatinine, and sodium levels were used in further analyses. Plasma levels of NT-proBNP were measured twice on admission before the initiation of any treatment and after clinical stabilization defined according to criteria described by Nohria et al. [22].

NT-proBNP level was measured in venous blood plasma by a sandwich immunoassay that used 2 polyclonal antibodies to epitope in the N-terminal part (1–76) of proBNP (1–108) (Elecsys 1010/2010 System, Roche Diagnostics GmbH, Mannheim, Germany). Analytical sensitivity was 5 pg/mL, CV of intra-assay and inter-assay precision was 1.8–2.7% and 2.2–3.2%, respectively, according to the data provided by the producer.

2.3. Clinical follow-up

Patients were regularly seen by the study investigators in the outpatient HF clinic, with a follow-up duration of ≥1 year. Information regarding survival was obtained directly from patients or their relatives, HF clinic database, or the hospital system. No patient was lost to follow-up. All-cause mortality was the primary end-point for the analyses.

2.4. Statistical analyses

Continuous variables were expressed as means ± standard deviations or percentages, where appropriate. The inter-group differences were tested using the unpaired Student's test, or the one-way analysis of variance ANOVA with post-hoc comparisons, where appropriate.

Plasma NT-proBNP level had a skewed distribution, and was expressed as medians with lower and upper quartiles. The inter-group differences in plasma NT-proBNP were tested using the Mann–Whitney U test, the χ^2 test, or the Kruskal–Wallis ANOVA, where appropriate. Correlations between plasma NT-proBNP and other variables were assessed using Spearman rank correlations (R).

The associations between analyzed variables and survival were assessed by Cox proportional hazards analysis (both single predictor and multivariable models). In the single predictor analysis, the following parameters were included as prognosricators: (1) age, sex, HF etiology (ischemic vs. non-ischemic); (2) history of co-morbidities (diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease); (3) clinical type of AHF according to the European Society of Cardiology classification [21]; (4) laboratory parameters on admission: levels of sodium, creatinine and hemoglobin; (5) need for inotropic support, and (6) plasma NT-proBNP levels on admission and after clinical stabilization (expressed in absolute units and as relative, percentage changes in NT-proBNP from admission). During the construction of multivariable models, we included all variables that had been shown to be significant predictors of survival in single predictor models. Forward and backward stepwise multivariate analyses were applied with $p=0.10$ used both for inclusion and exclusion of variables into the model. The assumptions of proportional hazard were tested for all the covariates.

In order to evaluate diagnostic accuracy of plasma levels of NT-proBNP in predicting death, we applied receiver operating characteristic (ROC) curve analysis for a 3- and 12-month follow-up with an estimation of area under curve (AUC), and established the cut-off values for percentage changes in NT-proBNP levels with the best sensitivity and specificity for a given time point. Kaplan–Meier curves for cumulative survival were constructed with the application of cut-off values established in ROC analysis. Differences in survival rates were tested using the Cox–Mantel log-rank test.

A value of $p<0.05$ was considered statistically significant. Statistical analyses were performed with StatView 5.0 for Windows (Abacus Concepts, Berkley, Calif) and Stata 9.1 (College Station, Tex).

3. Results

Baseline clinical characteristics of 103 patients with AHF are presented in Table 1.