

Prognostic factors of mid-term clinical outcome in congestive heart failure patients discharged after acute decompensation

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Abstract

Introduction: Risk stratification in congestive heart failure (CHF) patients is based on a variety of clinical and laboratory variables. We analysed renal function, BNP, water composition, echocardiographic and functional determinations in predicting mid-term outcome in CHF patients discharged after decompensation.

Material and methods: All subjects with NYHA class II-IV were enrolled at hospital discharge. NYHA class, BNP, water body composition, non-invasive cardiac output and echocardiogram were analysed. Death, cardiac transplantation and hospital readmission for CHF were scheduled.

Results: Two-hundred and thirty-seven (64.5% males, age 71.1 ±10.1) patients were discharged after obtaining normal hydration; left ventricular ejection fraction (LVEF) was 43.2 ±16.2%, cardiac output was 3.8 ±1.1 l/min and BNP at discharge resulted 401.3 ±501.7 pg/ml. During the 14-month follow-up 15 patients (6.3%) died, 1 (0.4%) underwent cardiac transplantation and 18 (7.6%) were readmitted for CHF (event group); in 203 (85.6%) no events were observed (no-event group). Higher NYHA class (2.1 ±0.7 vs. 1.9 ±0.4, $p = 0.01$), BNP at discharge (750.2 ±527.3 pg/ml vs. 340.7 ±474.3 pg/ml, $p = 0.002$) and impaired LVEF (33.7 ±15.7% vs. 44.5 ±15.8%, $p = 0.0001$) and creatinine (1.7 ±0.6 vs. 1.2 ±0.8 mg/dl, $p = 0.004$) were noticed in the event group. At multivariate Cox analysis LVEF ($p = 0.0009$), plasma creatinine ($p = 0.006$) and BNP at discharge ($p = 0.001$) were associated with adverse mid-term outcome. Kaplan-Meier survival curves demonstrated that adding cut-off points for creatinine 1.5 mg/dl and discharged BNP of 250 pg/ml discriminated significantly prognosis ($p = 0.0001$; log rank 21.09).

Conclusions: In predicting mid-term clinical prognosis in CHF patients discharged after acute decompensation, BNP at discharge ≥ 250 pg/ml added with plasma creatinine > 1.5 mg/dl are strong adverse predictors.

Key words: congestive heart failure, prognosis, natriuretic peptide.

Introduction

Risk stratification in patients suffering from chronic congestive heart failure (CHF) is based on a variety of clinical and laboratory variables. Indeed, several prognostic parameters have been identified, including age, New York Heart Association (NYHA) class, renal function, comorbidity such as atrial fibrillation, diabetes mellitus and ischaemic heart disease [1]. In acute decompensated heart failure (ADHF) episodes, the degree of renal dysfunction and arterial hypotension easily stratified patients with the

worst clinical outcome [2]. A single determination of brain natriuretic peptide (BNP) plasma level represents a reliable risk stratification procedure and its increase is considered a sensitive diagnostic marker of left ventricular dysfunction [3, 4]. Plasma BNP has clear prognostic relevance in predicting cardiovascular events in congestive heart failure (CHF) patients [5-8] and even in asymptomatic subjects [9].

The objective of this study was to analyse different prognostic parameters (renal function, plasma BNP, water composition, echocardiographic and functional capacity) in predicting mid-term clinical outcome in CHF patients discharged after an ADHF episode.

Material and methods

Patients

This prospective cohort study, approved by the local ethics committees, included patients admitted into the Heart Failure Unit from April 2008 to August 2010. All CHF subjects discharged after an acute episode of cardiac decompensation were enrolled in an out-patient clinic follow-up. Patients were classified as having CHF according to the criteria commonly accepted in the literature [10], namely the presence of 2 major criteria or 1 major criterion + 2 minor criteria according to the Framingham score and NYHA functional class II, III, or IV, due to exacerbation of symptoms with at least 1 class deterioration. The presence of inadequate echo images or no adherence to the therapy and disagreement with the periodical follow-up were considered exclusion criteria. All patients underwent a clinical examination, a 12-lead electrocardiogram, plasma determination of BNP, water composition (on admission and at discharge), 6-minute walk test (6MWT), non-invasive cardiac output and a transthoracic echocardiogram within 48 h upon hospital discharge. The criteria for discharging CHF patients were the following: a) subjective improvement on the basis of NYHA class, with no orthopnoea; b) $90 < \text{systolic blood pressure} < 120 \text{ mm Hg}$; c) heart rate $< 100 \text{ bpm}$; d) pulse oximetry in ambient air $> 90\%$; e) diuresis $> 1000 \text{ ml/day}$ [11] + obtaining normal hydration evaluated with bioelectrical impedance vectorial analysis (see below). Serum creatinine was checked on clinical stability. According to the study protocol, CHF out-patients were checked at 3 and 6 months after discharge. In case of worsening of the clinical status (worsening dyspnoea, body weight increase or oedema, cardiac arrhythmias), a clinical control was provided. The therapy prescribed in those patients included angiotensin-converting enzyme inhibitors (enalapril, ramipril), angiotensin receptor blockade (candesartan, losartan) in case of enalapril/ramipril

intolerance, β -blockers (metoprolol, bisoprolol or carvedilol), digoxin, loop diuretic and spironolactone at low dose. For β -blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockade, the patients' maximum tolerated dose was used, after an adequate titration period.

Doppler echocardiography

Echocardiograms were performed with a Vivid 7 computed sonography system (GE Medical Systems, Waukesha, Wisconsin, USA) according to the recommendations of the American Society of Echocardiography [12]. Two-dimensional apical 2- and 4-chamber views were used for volume measurements; LVEF was calculated with a modified Simpson's method using biplane apical (2- and 4-chamber) views. The left ventricular (LV) end-diastolic volume and the LV end-systolic volume were recorded. All the echo examinations were performed by expert operators blinded to the results of BNP assay; the intra-observer variability in the evaluation of left ventricular ejection fraction (LVEF) was found to be $< 5\%$. Echocardiographic measurements including LV end-diastolic diameter, and the diastolic thickness of the ventricular septum and the posterior LV wall were determined according to the American Society Echocardiography recommendations [12]. Systolic dysfunction was defined as a level of LVEF $< 50\%$. The definition of restrictive filling pattern (grade 3) was a predefined modification of classifications used in prior studies [13]: $E/A \geq 2$, $DT \leq 150 \text{ ms}$, $S/D \text{ ratio} < 1$, and $AR > 35 \text{ cm/s}$. All these criteria should be verified to define the restrictive filling pattern. The other diastolic filling patterns were classified as: grade 1 (abnormal relaxation) when $E/A < 1$ with $DT > 240 \text{ ms}$; grade 2 (pseudonormal) when E/A was $0.75\text{-}1.5$, DT was $160\text{-}240 \text{ ms}$ and $E/Ea > 15$ [13]. The Doppler sample was set 1-2 mm under the free edges of the mitral valve using the apical 4-chamber projection; an average of 5 beats was considered. In patients suffering from atrial fibrillation at the time of the echocardiogram, the diastolic function was classified as: 1) restrictive pattern ($DT \leq 150 \text{ ms}$) or 2) indeterminate ($DT > 150 \text{ ms}$). All these criteria should be verified to define the restrictive filling pattern: $\leq 150 \text{ ms}$, $S/D \text{ ratio} < 1$, and $AR > 35 \text{ cm/s}$. The presence of this diastolic pattern with $LVEF \geq 50\%$ was defined as an isolated diastolic dysfunction.

BNP assay

All blood samples were collected by venopuncture and immediately analysed with the bedside Triage B type natriuretic fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA). The Triage Meter is used to measure BNP concentration by detecting a fluorescent emission that reproduces the amount of BNP in the blood. Two hundred and

fifty microlitres of whole blood was added to the disposable device, then the cells were filtered and separated from the plasma with BNP, which entered a reaction chamber containing fluorescent BNP antibodies. After 2-min incubation, the BNP-antibody mixture migrated to an area containing immobilised antibodies and remained fixed. The unbound fluorescent antibodies were washed away by the excess sample fluid. Then, the Triage Meter measured the fluorescent intensity of the BNP assay area. The assay results were complete in 15 min. Performance characteristics of the test: assay range 5-5000 pg/ml; total CV 9.2-11.4%.

Non-invasive cardiac output

For the measurement of non-invasive cardiac output (CO), an inert gas rebreathing method (Innocor, Innovision A/S, Odense, Denmark) was used. The system utilised N₂O (blood soluble gas) and SF₆ (blood insoluble gas) enriched with O₂ of 0.5% and 0.1% respectively. Tidal volume was progressively increased in the closed circuit to match the physiological increase. Use of SF₆ allowed measurement of the volume of the lungs, valve and rebreathing bag. N₂O concentration decreases during the rebreathing manoeuvre, with a rate proportional to pulmonary blood flow. Three to four respiratory cycles were needed to obtain N₂O washout. Absence of pulmonary shunt was defined as arterial O₂ saturation > 98% (blood sample obtained from the arterial line). In the absence of pulmonary shunt, pulmonary blood flow = CO. This method was proved to be closely correlated with thermodilution (R = 0.93) and the direct Fick method (R = 0.94) [14].

Six-minute walk test

The 6MWT was performed on the day of discharge according to the guidelines of the American Thoracic Society [15]. The CHF patients able to walk underwent 6MWT if they did not meet the exclusion criteria (unstable angina and myocardial infarction during the previous month, resting heart rate > 120; systolic blood pressure > 180 mm Hg or diastolic blood pressure > 100 mm Hg). Repeat testing was performed after an adequate rest period in order to minimize the intraday variability.

Bioelectrical impedance vectorial analysis (BIVA)

Assessment of body fluid status was carried out using an electrical impedance analyser and Body-Gram 2.1 software (Akern Pontassieve, Florence Italy). The bioelectrical parameters of resistance, reactance and phase angle were obtained with an electric alternating current flux of 800 µA and an operating frequency of 50 kHz. Whole body impedance measurements were taken by using a standard position of outer and inner electrodes on the right hand and foot. The entire procedure was performed according to the indications of the National Institutes of Health Technology assessment conference statements [16]. Bioelectrical impedance evaluates some basic properties of the body by measuring resistance, reactance (a form of opposition that electronic components exhibit to the passage of the alternating current counterpart of direct current and which indicates an absolute amount of body cell mass). Bioelectrical impedance is normally used to estimate the volumes of body fluid com-

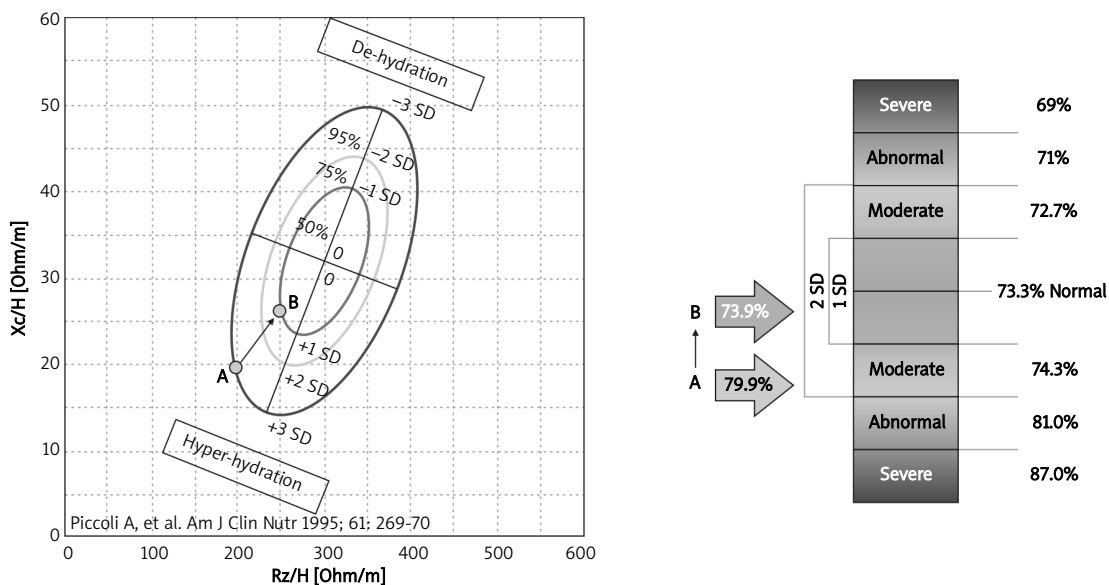


Figure 1. Evaluation of grade of hydration in CHF patients using the BIVA giagram and nomogram; on the left the same patients at time A presents hyper-hydration (+3 SD) that was reduced after diuretic therapy (point B)

partments allowing one to determine total body water and the ratio between extracellular and total body water. Resistance and reactance were always corrected for the patients' height. The clinical support of this method has been implemented using vector analysis (Bioelectrical Impedance Vector Analysis, Biavector) [17]. The backward or forward position of parallel vectors to the major axis of ellipses is normally correlated with dehydration or hyperhydration (Figure 1). The normal value of hydration was set at a value 73.3% (nomogram in Figure 1) and the area within +1 SD was considered a satisfactory criterion for discharging CHF patients.

Clinical follow-up

Death by any cause, cardiac transplantation and worsening heart failure requiring readmission to the hospital were considered cardiovascular events. Data regarding the occurrence of cardiovascular events were collected from multiple sources in all patients.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation (SD). We used the Mann-Whitney U-test and the Wilcoxon test for the comparisons between samples, while the association between variables was verified with Fisher's exact test. A *p* value < 0.05 was considered significant. Categorical variables (NYHA class, cardiovascular events) were analysed using the χ^2 test or Fisher's exact test. The Cox proportional hazard regression model was used to examine the relationship of clinical variables, BNP levels, and echocardiographic parameters with the incidence of the combined endpoint during the 6 months after discharge (hazard ratio and 95% confidence interval, CI). The hazard ratio for a continuous variable refers to the risk ratio per unit of the considered variable. The BNP levels were evaluated both as a continuous variable and as a categorical variable (based on cut-off values). According to the plasma BNP value, 2 groups were created, < 250 pg/ml and ≥ 250 pg/ml, in order to evaluate the role of different levels of plasma BNP on the occurrence of cardiac events in the follow-up. Survival curves were estimated according to Kaplan-Meier analysis and compared by the Tarone-Ware test. Analyses were performed using SPSS software for Windows, release 11.0, SPSS Inc., Chicago, USA.

Results

Two-hundred and thirty-seven patients with a diagnosis of CHF after an acute decompensation episode entered this cohort study. The mean age was 71.1 ± 10.1 years old (range: 30-89 years old); 64.1% were males (Table I). The main cause of CHF

was ischaemic heart disease (42%) followed by hypertensive and dilatative cardiomyopathy (Table I). In 12-lead electrocardiogram, 31% of patients were in permanent atrial fibrillation. On discharge the mean New York Heart Association functional class (NYHA) was 1.9 ± 0.5 and the mean plasma BNP was 401.3 ± 501.7 pg/ml. Renal function was generally impaired (serum creatinine 1.3 ± 0.8 mg/dl).

The transthoracic echocardiogram was performed on all subjects before discharge and a restrictive filling pattern was seen in 22% of participants, a pseudonormal pattern in 23% and an impaired relaxation in the majority (55%) of patients. The mean LVEF was $43.2 \pm 16.2\%$. Mild mitral regurgitation was found in 115 patients (48%), while 40 (16.8%) had moderate mitral regurgitation and 21 (8.9%) severe. The echocardiogram revealed mild or moderate aortic regurgitation in 15 patients (6.3%). Mild pericardial effusion was found in 18 subjects (7.5%), without any signs of haemodynamic significance. All the other clinical, biochemical and functional parameters are described in Table I.

The whole population was divided into an events group (34 [14.3%] subjects) and a no-event group (203 [85.7%] subjects) according to the occurrence of cardiovascular events.

The univariate statistical analysis demonstrated that patients in the events group manifested a reduced LVEF ($p < 0.01$), increased NYHA class ($p < 0.05$), a higher BNP plasma level on admission but also at discharge ($p < 0.01$) and impaired renal function ($p < 0.01$) compared to subjects in the no-event group (Table I). The water composition analysis demonstrated a higher fluid overload on admission in the event group ($p < 0.05$), a difference that disappeared at discharge after diuretic therapy. No differences were found in terms of non-invasive cardiac output and cardiac index at rest or in the 6MWT (Table I). It should be underlined that 8/34 patients in the events group were not able to perform the 6MWT because of confinement to bed or presenting a high degree of disability necessitating use of a wheelchair. It should be considered a limitation in the analysis of the test (see below).

Moreover, in the two groups no differences in terms of age, aetiology of CHF, or presence of atrial fibrillation emerged. The prescriptions of ACE inhibitors, angiotensin receptor blockers, and β -blockers showed a high prevalence, also considering the comorbidity (20% suffered from hypertension and 42% suffered from ischaemic heart disease) (Table I); patients were equally treated as regards other drugs (Table I). The amount of variation regarding the in-hospital reduction of plasma BNP (delta BNP; $p = 0.99$) or improved NYHA class (delta NYHA; $p = 0.3$) or, finally, amelioration of fluid overload (delta resistance; $p = 0.9$) did not dif-

Table I. Main clinical, echocardiographic and functional characteristics of patients with congestive heart failure

| Parameters | All (n = 237) | Events group (n = 34) | No-event group (n = 203) |
|--|------------------------|-----------------------|--------------------------|
| Age [years] | 71.1 ±10.1 (30-89) | 72 ±7.9 | 70.7 ±10.4 |
| Sex (M/F) [%] | 153/84 | 27/7 | 124/79 |
| NYHA on discharge | 1.9 ±0.5 (1-4) | 2.1 ±0.7 | 1.94 ±0.4* |
| Echocardiographic parameters | | | |
| LV ejection fraction [%] | 43.2 ±16.2 (10-77) | 33.7 ±15.7 | 44.5 ±15.8** |
| LV end systolic diameter [mm] | 46.5 ±23.6 (15-216) | 85.5 ±57.9 | 53.2 ±12.5** |
| LV end diastolic diameter [mm] | 57.2 ±25.6 (24-257) | 119 ±16 | 122 ±17** |
| Diastolic filling pattern % (I/II/III) | 55/23/22 | 23/12/65 | 62/25/13 |
| BNP admission [pg/ml] | 593.4 ±717.7 (80-5000) | 943.6 ±579.8 | 536.4 ±723.2** |
| BNP on discharge [pg/ml] | 401.3 ±501.7 (80-5000) | 750.2 ±527.3 | 340.7 ±474.3** |
| Serum creatinine [mg/dl] | 1.3 ±0.8 (0.5-8) | 1.7 ±0.6 | 1.2 ±0.8** |
| Haemoglobin [g/dl] | 12.2 ±1.9 (7-17) | 12.5 ±1.4 | 12.2 ±2 |
| Cardiac output [l/min] | 3.8 ±1.1 (1.6-6.4) | 3.7 ±1.4 | 3.8 ±0.9 |
| Cardiac index [l/min/mq] | 2.1 ±0.6 (0.9-3.7) | 1.9 ±0.7 | 2.1 ±0.5 |
| Resistance admission [ohm/mq] | 296.4 ±69.5 (177-517) | 274.8 ±59.2 | 303.3 ±71.7* |
| Resistance on discharge [ohm/mq] | 274.6 ±64.1 (157-425) | 259.5 ±69.5 | 281.4 ±61.2 |
| Reactance admission [ohm/mq] | 28.7 ±8.1 (11-57) | 28.4 ±9.5 | 28.8 ±7.6 |
| Reactance on discharge [ohm/mq] | 27.8 ±7.5 (13-46) | 28.7 ±7.6 | 27.4 ±7.5 |
| 6-min walk test on discharge [m] | 358.5 ±108 (80-540) | 347.1 ±82.8 | 359.6 ±110.6 |
| Delta NYHA | | 1.04 ±0.6 | 0.92 ±0.6 |
| Delta BNP [pg/ml] | | 245.1 ±310.8 | 245.04 ±599.1 |
| Delta resistance [ohm/mq] | | 5.2 ±63.3 | 7.2 ±70.3 |
| Main aetiology [%] | | | |
| Ischaemic heart disease | 42 | 67 | 55 |
| Hypertension | 20 | 10 | 13 |
| Idiopathic | 14 | 9 | 10 |
| Valvular heart disease | 24 | 16 | 22 |
| Other comorbidities [%] | | | |
| Atrial fibrillation | 31 | 35 | 30 |
| Diabetes mellitus | 34 | 58 | 31 |
| Treatment [%] | | | |
| ACE inhibitors | 78 | 80 | 76 |
| β-Blockers | 69 | 70 | 67 |
| Angiotensin receptor blockers | 15 | 16 | 14 |
| Digoxin | 55 | 63 | 52 |
| Spirolactone | 57 | 53 | 59 |
| Diuretics | 92 | 94 | 87 |

The values are expressed as mean + standard deviation, unless otherwise specified. Delta NYHA – NYHA discharge-NYHA admission, delta BNP – BNP admission-BNP discharge, delta resistance – resistance admission-resistance discharge. The ranges of values are reported in parentheses. *p < 0.05, **p < 0.01 Pearson χ^2

ferentiate between CHF patients who experienced cardiovascular events or not (Table I). The follow-up of this study lasted 408 ±255 days. During the 14-month follow-up 15 patients (6.3%) died, one

(0.4%) underwent cardiac transplantation and 18 (7.6%) were readmitted for CHF (events group); in 203 (85.6%) no events were observed (no-events group).

In multivariate Cox analysis only LVEF ($p = 0.0009$), plasma creatinine ($p = 0.006$) and BNP at discharge ($p = 0.001$) were significantly associated with adverse mid-term outcome. Age ($p = 0.6$) and the admission value of plasma BNP ($p = 0.05$) were not significantly correlated with clinical outcome. The Kaplan-Meier survival curves demonstrated that an LVEF < 40 or $\geq 40\%$ and a left ventricular end-systolic diameter (LVESD) of < 47 mm or ≥ 47 mm influenced prognosis ($p = 0.04$; log rank 4.2 and $p = 0.002$, log rank 9.15 respectively) (Figures 2-3) and that a stratification according to serum creatinine (< 1.5 mg/dl, 1.5-2 mg/dl or > 2 mg/dl) identified three different event-free curves ($p = 0.00001$, log rank 28.76) (Figure 4). In Figures 5 and 6 the event-free curves are depicted according to the plasma value of BNP at admission or at discharge (value < 250 pg/ml or ≥ 250 pg/ml), showing a significant predictive val-

ue for the discharge value ($p = 0.001$, log rank 10.7 at discharge, $p = 0.05$, log rank 3.7 at admission). In Figure 7, significantly different event-free curves according to the three diastolic filling patterns (type 1-3) emerged ($p = 0.0001$, log rank 22.44). Finally, adding two parameters (creatinine $<$ or > 1.5 mg/dl and BNP $<$ or > 250 pg/ml), four different survival curves were obtained ($p = 0.0001$; log rank 21.09), in which the clinical significance of renal function clearly emerged (Figure 8).

Discussion

From this study it emerged that CHF patients discharged after an acute decompensation had a severe adverse clinical outcome (death, cardiac transplantation and hospital readmission) in 14.3% during a follow-up lasting 14 months. Elderly

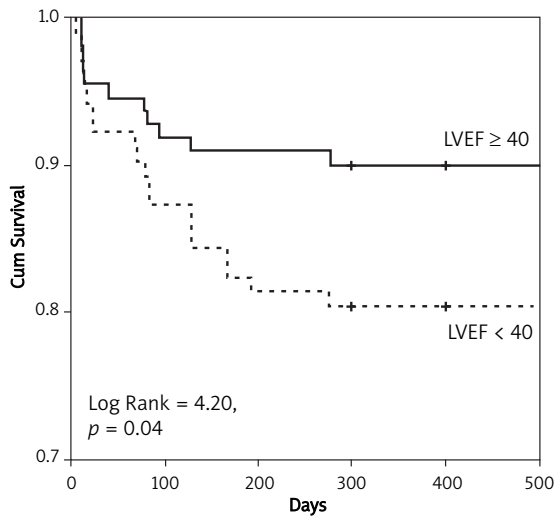


Figure 2. Event-free curves in CHF patients according to the LVEF

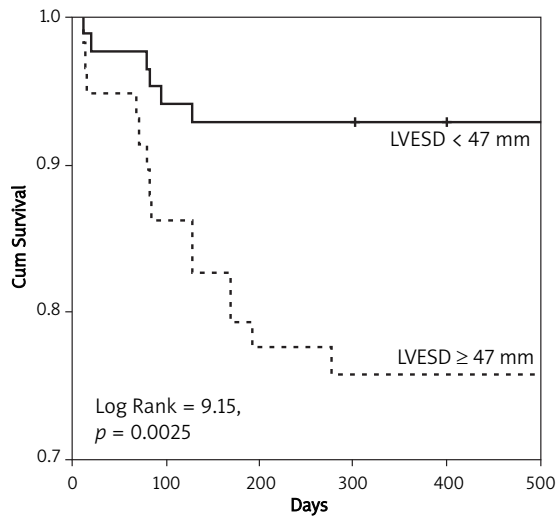


Figure 3. Event-free curves in CHF patients according to the left ventricular systolic diameter

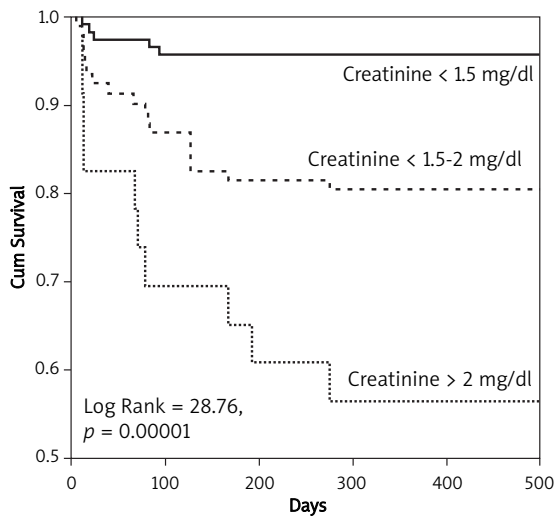


Figure 4. Event-free curves in CHF patients according to plasma creatinine

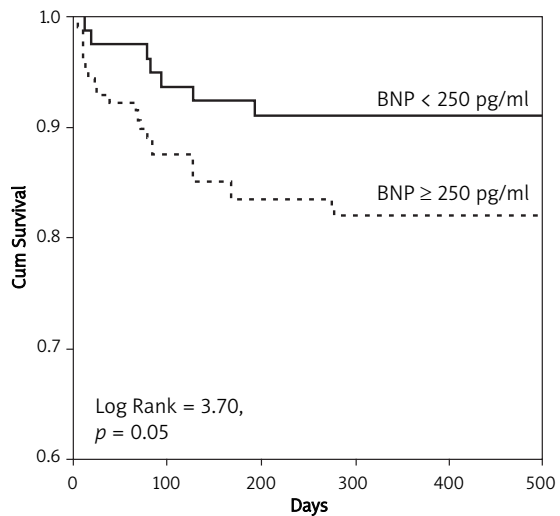


Figure 5. Event-free curves in CHF patients according to plasma BNP at admission

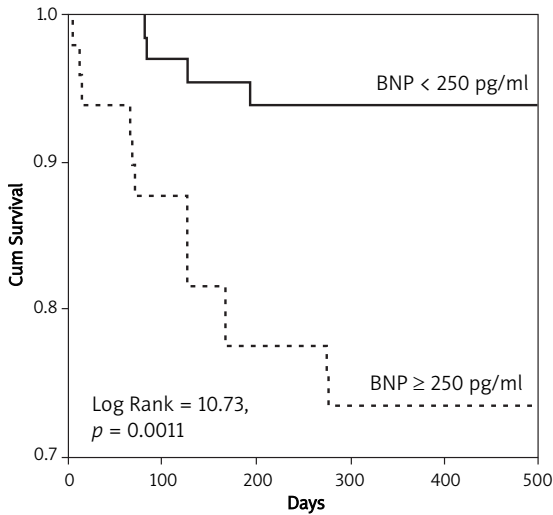


Figure 6. Event-free curves in CHF patients according to plasma BNP at discharge

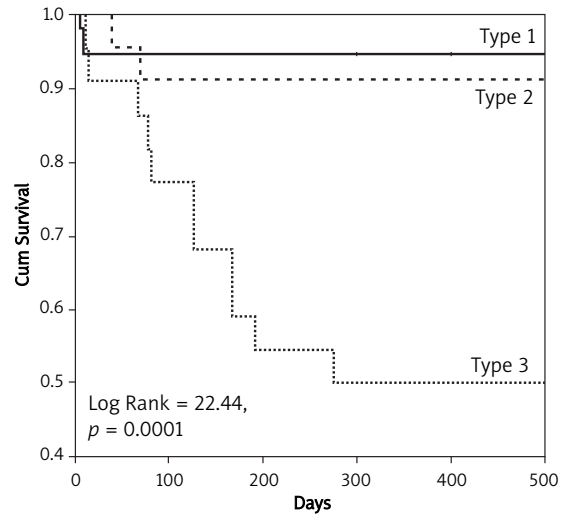


Figure 7. Event-free curves in CHF patients according to diastolic filling pattern obtained with transthoracic echocardiography before discharge

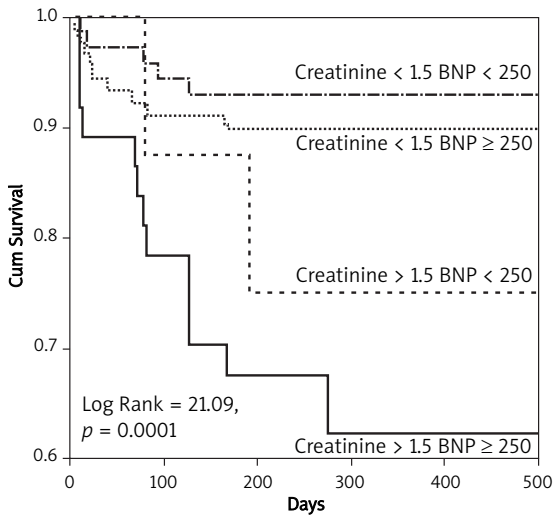


Figure 8. Event-free curves in CHF patients according to plasma BNP at discharge added to serum creatinine

patients with CHF represent most subjects (70%) admitted to hospitals for acute cardiac decompensation; the length of hospitalization lasts usually > 2 weeks in geriatric wards and readmission is frequent [18]. Recently, the OPTIMIZE-HF study [19], which included more than 30 000 CHF patients discharged from 215 hospitals, described a short length of hospitalization (4 days) but a 21.3% rate of readmission within 30 days. The study showed that an early (one-week) outpatient clinical follow-up after discharge resulted in a lower probability of being readmitted within 30 days. Considering the huge number of CHF patients discharged from our hospital, easy and practical prognostic parameters able to predict adverse outcomes are essential in order to allocate our resources correctly.

The first strong prognostic parameter in those patients was a plasma BNP value at discharge ≥ 250 pg/ml ($p = 0.001$, log rank 10.7). This confirms previous reports [8, 20] in which the pre-discharge values of BNP identified an adverse outcome (death or hospital re-admission) at 6-month follow-up. According to the practical approaches to treating CHF patients published by Maisel [21], there could be identified a ‘wet BNP’ in patients with CHF and fluid overload and a ‘dry BNP’ after optimization of therapy. In our population only the ‘dry BNP’ (at discharge) predicted cardiovascular events, because it identified the real state of neurohormonal modulation due to systolic/diastolic heart dysfunction and left ventricular enlargement. This was confirmed by the lack of significance of the amount of reduction of plasma BNP during hospitalization (delta BNP), which might be translated as: what matters is not how much the optimized therapy has reduced the BNP of your patient, but what is the value at discharge.

The second strong predictor of adverse outcome was renal dysfunction. The presence of a chronic cardio-renal syndrome, recently classified as type 2 of the cardio-renal syndromes [22], has been reported in 63% of patients admitted for CHF [23, 24]. Moreover, the ADHERE registry highlighted that the in-hospital mortality risk increased considerably in patients with urea nitrogen ≥ 43 mg/dl and plasma creatinine ≥ 2.75 mg/dl [25]. In our population serum creatinine was higher in the event group ($p < 0.01$) and alone identified (divided into three groups: < 1.5 mg/dl, 1.5-2 mg/dl and > 2 mg/dl) three different cumulative survival curves (Figure 4). Moreover, adding data of renal function with discharge plasma BNP, four different cumulative survival curves emerged (BNP < 250 pg/ml and creatinine < 1.5 mg/dl, BNP < 250 pg/ml and creatinine

> 1.5 mg/dl, BNP > 250 pg/ml and creatinine < 1.5 mg/dl, and BNP > 250 pg/ml and creatinine > 1.5 mg/dl (Figure 8), in which there clearly appeared the prognostic significance of serum creatinine > 1.5 mg/dl. Therefore, this analysis identified a simple and practical combination of two markers for identifying a high-risk CHF patient at discharge for a medium-term follow-up, which should be strictly monitored and controlled in order to avoid adverse clinical outcome. Clinicians whose take care of CHF patients might predict different clinical outcome combining two simple and inexpensive parameters (plasma BNP and plasma creatinine).

Finally, this study confirmed the prognostic significance of simple echocardiographic parameters, such as LVEF, left ventricular end-systolic diameter (LVESD) and the diastolic filling pattern. In the ESC Guidelines on chronic heart failure [26], the left ventricle was defined as enlarged when the end-systolic diameter was > 45 mm. In patients who survived a myocardial infarction [27] and in cardiomyopathies [28], LV diameters obtained with M mode had strong value for predicting cardiovascular death in long-term follow-up. In our population, the cut-off of 47 mm for LVESD guaranteed a significant powerful stratification for cardiovascular events. The prognostic role of mitral pattern inflow in CHF subjects was highlighted in the meta-analysis of Whalley *et al.* [29], in which a mortality rate of 22.7% and an odds ratio for all-cause mortality of 4.36 emerged (average follow-up between 3 months and 5 years). In CHF patients with idiopathic dilated cardiomyopathy, the presence of a restrictive filling pattern was associated with a six-fold (OR 6.65) increase in mortality. The mortality rate in post-MI patients with a restrictive pattern in the echocardiogram was 31.8% (average follow-up between 2 weeks and 5 years) with a calculated odds ratio of 4.10 [30]. The presence of a pre-discharge restrictive filling pattern in CHF patients after an acute episode of cardiac decompensation corresponded to a high short-term mortality (14%) and readmission rate (42.4%) [31]. Data obtained in this study underlined the importance of the echocardiographic assessment of diastolic filling pattern in CHF patients, able to differentiate prognosis in type 3 vs. the non-restrictive pattern ($p = 0.0001$; log-rank 22.44) and providing robust prognostic information. Finally, this experience failed to demonstrate clinical predictive value of non-invasive determination of CO or SV (Definition missing) at rest, that might be tested during exercise in order to discriminate exercise limitation due to left ventricle pump failure [32].

In conclusion, in CHF patients discharged with bioimpedance evidence of normal hydration after an episode of acute decompensation, plasma BNP \geq 250 pg/ml and mild renal impairment seemed to

be the strongest predictor of mid-term adverse outcome. Simple echocardiographic parameters (LVEF, LVESD and diastolic filling pattern) might help in determining clinical outcome.

In the interpretation of the 6MWT results the complete inability of 23.5% of patients in the events group to perform the test might be underestimated. In fact, Passantino *et al.* [33] demonstrated that the increase in walking distance was significantly associated with survival in CHF patients who walked < 340 m at baseline, confirming the highly prognostic value of 6MWT in those patients.

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