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ORIGINAL ARTICLE

NT-ProBNP at Admission Versus NT-ProBNP at Discharge as a Prognostic Predictor in Acute Decompensated Heart Failure

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Abstract

Background: Patients admitted for decompensated heart failure (HF) receive intensive diuretic and vasodilator therapy in the first days. Normally, this is a successful approach that leads to HF compensation and hospital discharge. However, recurrences within the first week of discharge are common.

Objective: to evaluate whether the main predictor of recurrent outcomes in patients with HF is the severity of decompensation at admission or patient's blood volume after clinical management.

Methods: Prospective, cohort study of patients admitted between January 2013 and October 2014, with diagnosis of acute decompensated HF, who were followed-up for 60 days after discharge. Inclusion criterion was increased plasma NT-proBNP (> 450 pg/mL for patients younger than 50 years or > 900 pg/mL for patients older than 50 years). Primary outcome was the combination of cardiovascular death with rehospitalization for decompensated HF in 60 days.

Results: Ninety patients were studied, with median NT-proBNP at admission of 3,947pg/mL (IQR: 2,370 – 7,000 pg/mL), and median NT-proBNP at discharge of 1,946pg/mL (IQR: 1,000 – 3,781 pg/mL). The incidence of combined outcome was 30% (12.2% of deaths and 20% of rehospitalization). The area under the ROC curve for NT-proBNP at admission and 60-day cardiovascular events was 0.49 (p = 0.89; 95% CI = 0.36 – 0.62). The area under the curve of NT-proBNP absolute variation for 60 day-events was 0.65 (p = 0.04; 95%CI = 0.51 – 0.79), and the area under the curve for NT-BNP at discharge was 0.69 (p = 0.03; 95%CI = 0.58 – 0.80). In the multivariate analysis, pre-discharge NT-proBNP was a predictor of the primary outcome, independently of the NT-proBNP at admission and other risk factors.

Conclusion: Different from the severity of decompensation at hospitalization, blood volume after compensation of HF is associated with recurrent event. This finding suggests that, regardless of initial severity, therapy response during hospitalization is determinant of the risk of recurrent decompensation. (Int J Cardiovasc Sci. 2017;30(6)469-475)

Keywords: Heart Failure / therapy; Heart Failure / mortality; Ventricular Dysfunction; Natriuretic Peptide; Hospitalization.

Introduction

Acute decompensated heart failure (ADHF) is the main cause of hospitalization in individuals older than 65 years.[1] Usually, the use of intravenous diuretics and vasodilators during hospitalization promotes a rapid relief of congestive HF. Nevertheless, hospitalization rate is high. Thus, it is important to identify mechanisms of symptom recurrence after hospital discharge, in order to determine whether the major triggering factor is the severity of initial decompensation or the capacity of patients to respond to the therapy.

Plasma concentration of NT-proBNP (N-terminal of the prohormone brain natriuretic peptide) reflects alteration of blood volume regulation in patients with ADHF, with a positive correlation with pulmonary capillary pressure.[2-4] Besides, the reduction in NT-proBNP levels directly reflects blood volume response to diuretic therapy.[5-7]

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With the aim of assessing the prognostic role of blood volume in both clinical decompensation at hospital admission and clinical compensation at discharge, plasma levels of NT-proBNP were measured in 90 consecutive patients admitted to a cardiac intensive care unit.

Methods

Sample selection

Patients with diagnosis of ADHF consecutively admitted to a cardiac unit of a tertiary hospital between January 2013 and October 2014 were included in the Heart Failure Registry. The inclusion criteria to this registry are the increase in plasma NT-proBNP (> 450 pg/mL in patients younger than 50 years or > 900 pg/mL for patients older than 50 years), and the presence of at least one of these characteristics: 1) dyspnea at rest or in the last 15 days; 2) signs of low cardiac output (hypotension – systolic blood pressure < 90 mHg; oliguria – urine output < 0.5 mL/kg/h; decreased level of consciousness); 3) signs of right heart failure (hepatomegaly, edema in lower limbs, jugular vein stasis). Exclusion criteria included age under 18 years, pregnancy, or refusal to participate in the study. The study was approved by the Ethics Committee of the institution, and all patients signed the informed consent form.

Determination of NT-proBNP plasma levels

NT-proBNP plasma levels were determined in blood samples collected as soon as the patient was admitted to the emergency, to obtain the shortest time between the onset of symptoms and blood collection. Another measurement was performed when the patient was clinically stable according to physician's judgment and able to be discharged. NT-proBNP measurements were performed in serum by ELFA (Enzyme-Linked Fluorescent Assay).

Cardiovascular outcomes

Primary outcome was defined as 60-day cardiovascular death and/or rehospitalization by decompensated heart failure. Patients' follow-up was performed during hospitalization and by telephone interview for assessment of combined symptoms at day 60 after discharge. Cardiovascular death was defined as sudden death or heart failure decompensation.

Statistical analysis

NT-proBNP values were expressed as median and interquartile range (IQR) and, as they were normally distributed, between-group comparisons were performed by the Mann-Whitney test. Analysis of NT-proBNP as a prognostic factor for cardiovascular outcomes in 60 days was performed by analysis of the area under the ROC (Receiver Operating Characteristics – ROC) curve. We also evaluated values of plasma NT-proBNP at hospital admission and discharge, as well as the absolute variation (difference between NT-proBNT at admission and NT-proBNT at discharge).

NT-proBNT was adjusted for clinical variables of death and rehospitalization for ADHF by logistic regression. First, an exploratory analysis of predicting variables was conducted, and then these variables were inserted into the model by the backward method. Kaplan Meier survival curves were plotted for patients with NT-proBNT levels above and below the median, and compared by the Log-rank test. Statistical significance was set at $p < 0.05$. Spearman correlation test (non-parametric test) was also conducted between NT-proBNT at admission and NT-proBNT absolute variation. Analyzes were performed by the SPSS software version 17.0 (SPSS Inc., Chicago, USA).

Sample size calculation

Sample size was estimated for adequate statistical power of pre-established analyzes, and to obtain a statistically significant ROC curve, with an area under the curve of 0.75 and event rates of 25%. A pilot study was conducted with the first 30 patients, and we found an event rate of 30%.

Results

Sample characteristics

A total of 90 patients (55% men) with diagnosis of ADHF, aged 69 ± 16 years were studied; 92% of them had dyspnea as a symptom of decompensation, and 95% were hospitalized with NYHA (New York Heart Association Functional Classification) class III/IV. Mean hospitalization period was 5 days. Ischemic heart disease was found in 50% of patients, and 49% of the sample had left ventricular ejection fraction (LVEF) lower than 40%. Among the causes of decompensation, low

adherence to treatment was found in 41% of patients, and infection in 21% of patients. Median NT-proBNT at admission was 3,947 pg/mL (IQR: 2,370 – 7,000 pg/mL). Median absolute variation between admission and reversal of decompensation was –1533 pg/mL (IIQ = –3569 – 747 pg/mL), whereas NT-pro-BNP at discharge was 1,946 pg/mL (IIQ = 1000 – 3781 pg/mL).

During hospitalization, all patients received intravenous diuretics, 46% received angiotensin-converting-enzyme inhibitor, 36% received angiotensin receptor blockers, 71% received beta-blockers, 48% received intravenous nitroglycerin and 9% dobutamine. Other clinical features are described in Table 1.

During the first 60 days of admission, there was an incidence of 30% (n = 30) of combined cardiovascular events, 12.2% (n = 11) deaths in the first hospitalization (index hospitalization), and 20% (n = 18) of readmissions for heart failure.

Association between NT-proBNP and cardiovascular events

Median NT-proBNP at admission was similar between the patients free from events (3,341 pg/mL; IQR: 2,338 – 7,464 pg/mL) and those who had outcomes during the 60 days of follow-up (4,000 pg/mL; IQR = 2,376 – 6,927 pg/mL; p = 0.81). Also, the area under the ROC curve for NT-pro-BNP as an event predictor was 0.49 (95%IC: 0.36 – 0.62; p=0.89), suggesting the absence of predictive value (Figure 1A). Cardiovascular event-free survival was similar between the groups with NT-pro-BNP above the median and those with NT-pro-BNP below the median (67% *vs* 63%; p = 0.89; HR =1.07; 95%CI = 0.47 – 2.41; p = 0.86).

Regarding NT-proBNP variation, the absolute reduction was greater in the group free of cardiovascular events (- 2300 pg/mL; IQR: –4024 to –508 pg/mL) than in the group with outcomes after discharge (–1040 pg/mL; IQR = –2500 to – 832 pg/mL; p = 0.018). According to the area under the curve, the performance of NT-proBNP was 0.65 (95%CI: 0.53 – 0.77; p = 0.04) (Figure1B). Event-free survival was statistically different between the groups with absolute NT-proBNP variation above and below the median (52% *vs* 80%; p = 0.07; HR = 0.35; 95% CI = 0.16 – 0.78; p = 0.01).

NT-proBNP levels at discharge were higher among patients who required rehospitalization (2,300 pg/mL; IQR = 1,400 – 4,007 pg/mL), as compared with those free of events (1,489 pg/ml; IQR = 800 – 2,900 pg/ml; p = 0.003). The performance of this variable according to the area under the ROC curve was 0.69 (95% CI: 0.58 – 0.81; p = 0.03) (Figure 1C). Event-free survival was statistically different between the groups with NT-proBNP above and below the median (53% vs 78%; p = 0.01; HR = 0.097; 95% CI = 0.013 – 0.71; p = 0.02) (Figure 1D).

There was a strong correlation between NT-proBNP at admission and the absolute variation during hospitalization (r= – 0.86; P=0.001), suggesting that these values may influence the medical approach to the negative water balance (Figure 2).

Multivariate analysis

In logistic regression analysis of both NT-proBNP at discharge (OR = 1.003; 95%CI = 1.0007 – 1.001; p = 0.009) and NT-proBNP absolute variation (OR = 1,001; IC 95% = 0,999 – 1,002; p = 0,17), NT-proBNP at discharge was an independent predictor, regardless of outcome occurrence, whereas the absolute variation lost its significance, which suggests that blood volume prior to hospital discharge is the strongest determinant.

In the second logistic regression model, we tested the predictive value of NT-proBNP at discharge, independently of the variables likely to have a causal effect on the outcome. Covariables included in the model were age, creatinine, and LVEF. After adjustment of the model, NT-proBNP at discharge (OR = 1.002; 95% CI = 1.001 – 1.003; p = 0.027) and creatinine (OR = 6.03; 95%CI = 2.63 – 13.8; P = 0.001) remained associated with the outcome, whereas age and LVEF lost its statistical significance (Table 2).

Discussion

The present study suggests that blood volume variation during hospitalization is more important than blood volume at admission for the prognosis of patients with ADHF. NT-proBNP at discharge, resulting from the clinical approach during hospitalization, was the strongest prognostic factor.

Different from studies with a blind design, in the present study in which the medical staff had access to the NT-proBNP values, the severity of decompensation at admission was not associated with any of the outcomes. The strong correlation between NT-proBNP at admission and its decrease suggests the possibility that the NT-proBNP levels were used as a base for therapy intensity, resulting in a greater reduction in blood

Table 1 – General characteristics of the sample

Variables (n = 90)	
Clinical data	
Age (years) (mean and SD)	69 ± 16
Male sex	50 (55%)
Systolic blood pressure (mmHg)(mean and SD)	150 ± 35
Heart rate (bpm) (mean and SD)	92 ± 30
Creatinine (mg/dl)(mean and SD)	1.2 ± 0.6
Urea (mg/dl)(mean and SD)	60 ± 30
Prognostic score	
ADHERE (median and IQR)	– 3 (IQ = – 3.6 a – 2.2)
OPTIMIZE (mean and SD)	35 ± 6
Heart failure etiology	
Ischemic	45 (50%)
Hypertensive	18 (20%)
Chagasic	3 (3%)
Others	24 (27%)
Left ventricular ejection fraction	
< 40%	43 (49%)
> 40%	42 (47%)
Therapy during hospitalization	
ACEI	32 (46%)
ARB	25 (36%)
Beta-blockers	50 (71%)
Spironolactone	19 (27%)
Furosemide	90 (100%)
Digitalis	16 (23%)
Hydralazine	15 (21%)
Nitrate	30 (43%)
Dobutamine	6 (9%)
Nytroglicerin	34 (48%)
Nitroprusside	6 (9%)
Values of NT-proBNP	
At admission	3,947 (IQ = 2,370 a 7,000)
Absolute variation	–1,533 (IQ = – 3,569 a 747)
Discharge	1,946 (IQ = 1,000 a 3,781)
60-day cardiovascular outcomes	
Combined (cardiovascular death and rehospitalization)	30 (34%)
Cardiovascular deaths after discharge	8 (9%)
Rehospitalization	22 (24%)

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

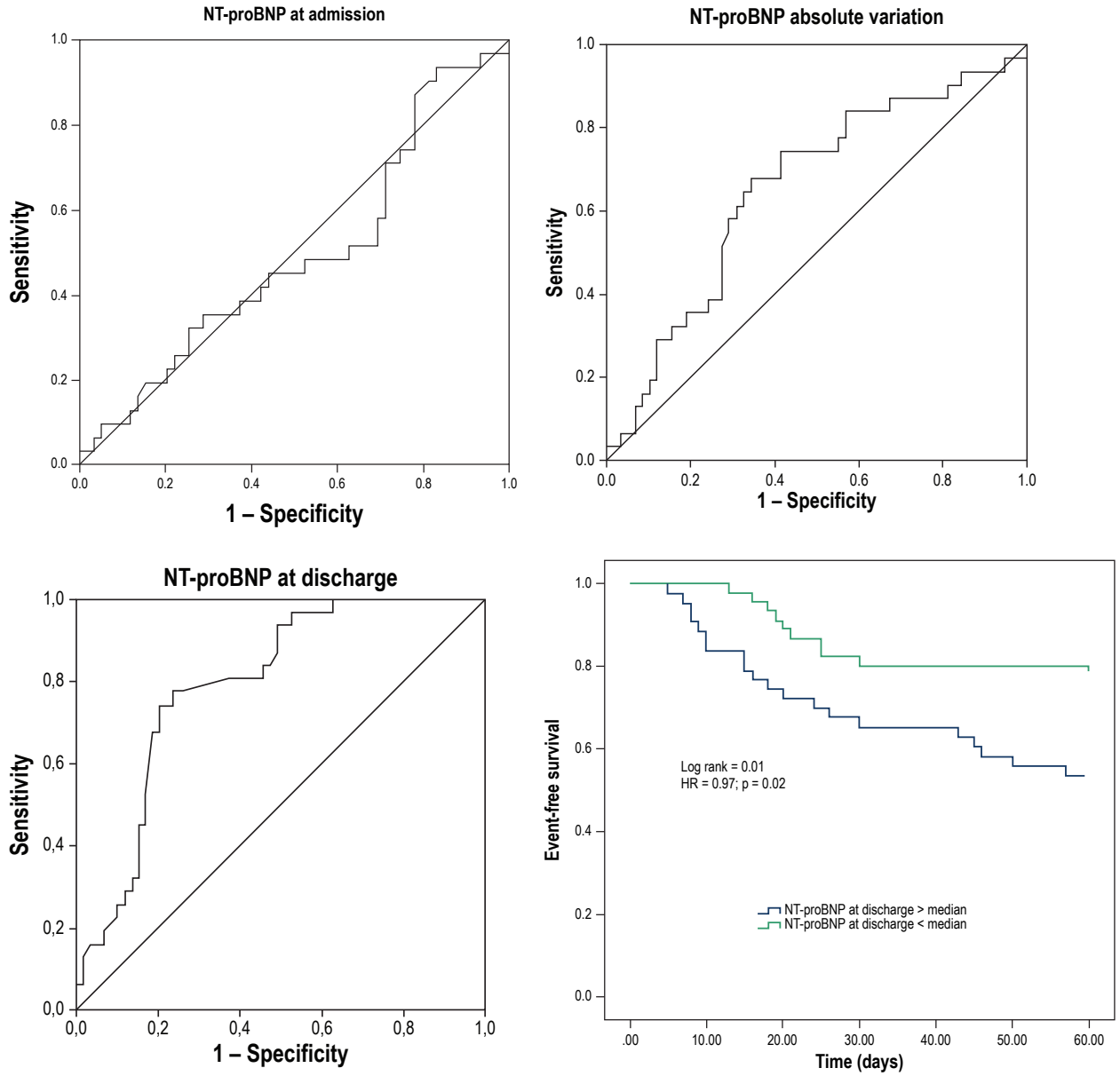

Figure 1 – *ROC curve of combined events – 60-day mortality and rehospitalization. NT-proBNP at admission (A); NT-proBNP absolute variation (B); NT-proBNP at discharge (C); Kaplan Meier curve of events or discharge b NT-proBNP at discharge (above or below the median)*

volume. Besides, it is possible that hypervolemic patients are more responsive to diuretic therapy, regardless of the dose applied.

Our results are similar to those reported in an unblinded study by O'Brien et al.,[8] which showed that NT-proBNP at discharge, rather than admission, acts as a predictor of adverse prognosis following acute left ventricular failure. A recent systematic review suggests that few studies with high methodological quality has been performed in this area, which emphasizes the importance of our study.[9]

In our analysis, another predictor factor of cardiovascular events was serum creatinine at admission, as demonstrated in previous studies.[10] Changes in renal filtration are recognized as prognostic markers in heart failure patients. Multiple mechanisms, not fully elucidated, may explain this finding, since some of these patients already have pre-existing lesions. Another mechanism is cardiorenal syndrome type 1, which is the acute renal injury secondary to decompensated heart failure.

One limitation of this study is its single-center design which limits the generalization of the results. For a better

Table 2 – Logistic regression with NT-proBNP adjusted for the risk factors for combined events (death or rehospitalization)

Variables	OR (95%CI)	p-value
Age	2.69 (0.94-7.62)	0.85
Creatinine	6.03 (2.63-13.8)	0.001
Left ventricular ejection fraction	1.005 (0.956-1.056)	0.72
NT-proBNP at discharge	1.002 (1.001-1.003)	0.02

analysis, an interaction test should be performed between reduced LVEF and NT-proBNP, but such analysis was not possible due to small sample size. Besides, analyses of creatinine levels at discharge and its variation during hospitalization should also be performed for a better evaluation of this variable, similarly to what was performed with NT-proBNP.

From a clinical standpoint, the present study suggests that the therapy should focus on blood volume optimization before hospital discharge. This can be performed by assessment of cumulative water balance, change of body weight and radiologic data as well. On the other hand, due to its objectivity, NT-proBNP may be an important parameter of blood volume control before discharge, since there are limitations in the clinical examination for subclinical congestion.

Conclusion

Different from the severity of decompensation at hospitalization, blood volume after compensation of heart failure is associated with recurrent events, as evaluated by NT-proBNP plasma levels. This finding suggests that therapy response during hospitalization, rather than initial severity, was determinant of recurrent decompensation within 60 days of hospital discharge. This hypothesis should be confirmed by randomized clinical trials that investigate the use of NT-proBNP during hospitalization.

Author contributions

Conception and design of the research: Magalhães J., Soares F., Correia L. Acquisition of data: Magalhães J. Analysis and interpretation of the data: Soares F. Statistical analysis: Soares F. Writing of the manuscript: Noya M. Critical revision of the manuscript for intellectual content: Noya M. Supervision / as the major investigador: Niemann G., Andrade L.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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