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Article

Difference between Serum BNP Admission Level and that Detected at Discharge in Patients with ADHF Predicts Six-Month Mortality in a More Reliable Manner with Respect to Isolated BNP Determination Taken on Admission

Running Title: BNP Rising at Discharge as an Ominous Predictor in HF Patients

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Abstract: Background According to some authors, a single isolated measurement of serum BNP executed on hospital admission would not be a sufficiently accurate method to predict the outcome of patients with ADHF. **Aims** For verifying this assumption, a retrospective study was conducted on patients hospitalized for ADHF. Our main objective was to ascertain whether there was any difference in midterm mortality among patients with rising BNP at discharge as compared to those with decreasing BNP at discharge. **Methods** Medical records were examined so as to make a partition of the ADHF patient population into two groups, the former characterized by a rise in BNP during hospitalization, and the latter exhibiting a decrease in BNP in the measurement taken at hospital discharge. **Results** 177 patients were enrolled in a retrospective study. Among them, 53 patients (29.94%) had increased BNPs at the time of discharge, whereas 124 (70.06%) showed decreases in serum BNP during their hospital stay. The group with patients who exhibited BNP increases at the time of discharge had higher degree of congestion evident in the higher frequency of persistent jugular venous distention and persistent orthopnea at discharge. Moreover, patients with increased BNP at the time of discharge had a lower reduction in inferior vena cava maximum diameter [1.58 ± 2.2 mm vs. 6.32 ± 1.82 mm; p (one-way ANOVA)=0.001]. In contrast, there was no significant difference in weight loss when patients with increased BNP at discharge were compared to those with no such increase. A total of 14 patients (7.9%) died during the six-month follow-up period. Cox proportional hazard analysis revealed that BNP increase at the time of discharge was an independent predictor of six-month all-cause mortality after adjustment for age, sodium at discharge, creatinine at discharge and New York Heart Association (NYHA) class at discharge (hazard ratio 34.49; 95% confidence intervals: 4.55–261.06; P =0.001). **Conclusions** Among patients with history of ADHF, more elevated BNP levels at the time of discharge from the hospital compared to those detected at admission identify a patient subset with higher grade of congestion and higher six-month mortality.

Keywords: natriuretic peptides; heart failure; congestion; outcome

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Introduction

Prognostic studies have shown that serum BNP values, measured after treatment were more predictive of post-discharge mortality and cardiovascular events, compared to the values recorded at the time of admission (1). Moreover, Cohen–Solal and coll. found that patients with a fall of the BNP serum level , especially when occurring on the fifth day after onset of therapy, had a reduced risk of mortality in despite of a BNP value detected at admission significantly higher than that found in the other patients (2). Increased BNP in hospital is sometimes detected, by comparing values found at admission with those seen at discharge, despite the appropriate treatment of acute HF, suggesting that there may be other determinants able to influence the level of serum BNP (3) in addition to the decisive main factor that is the grade of hemodynamic overload of the ventricular myocardium**.**

Aims

In this study, we aimed to detect the characteristics and outcomes of patients hospitalized for ADHF, all characterized by values of BNP at discharge that were higher than those found at admission. This group of patients with BNP rising at discharge were compared with other patients similarly affected by ADHF who instead had exhibited a BNP reduction at the end of hospital stay compared to the admission values. Other study objectives included determining the characteristics and grade of congestion of patients with BNP increase at the time of discharge in comparison with those who had a reduction of discharge BNP.

Methods

In this retrospective study, all data were collected from paper or electronic medical records related to the activities of hospitalization and subsequent follow-up of patients with confirmed diagnosis of acute decompensated heart failure (ADHF) who belonged to the Division of Cardiology of the Clinic "Sollievo della Sofferenza" of San Giovanni Rotondo(Italy) during the period from January 2012–January 2015. For inclusion in our retrospective study, the patients were required to have received a diagnosis of ADHF entailing hospitalization. Moreover, both the BNP value measured at the time of hospital admission as well as the value of BNP corresponding to the time of discharge should have been reported in the medical sheets in order to comply with the aims of the study. Finally, for each patient included in our retrospective study, availability of clinical follow-up data concerning the first six months after discharge was required. Pertaining data were collected with the consent of the Hospital Directorate ; they derived from careful evaluation of clinical records, in strict accordance with the rules and regulations that apply to the patient's privacy preservation.

In this retrospective study, our primary endpoint was six-month all-cause mortality. Among the signs deduced from physical examination, we used jugular venous distention (JVD) and orthopnea for assessing and grading volume status, according to other Authors (4-5) . In addition, we used further two objective variables, recognized suitable to evaluate decongestion (6-8): weight loss and reduction in the inferior vena cava (IVC) maximum (i.e., expiratory) diameter from admission to discharge.

Statistical analysis Patients with or without BNP increase at discharge were compared as regards their main signs and symptoms of clinical congestion as well as with respect to the mortality at six months. Continuous variables were expressed as mean ± standard deviation and were tested for normality of distribution using the D'Agostino–Pearson test. They were compared using one-way analysis of variance (ANOVA) and/or independent samples t-test for normally distributed variables, or using Mann–Whitney U test for non-normally distributed variables. Paired sample t-test was used to compare the grade of congestion within each group on admission and discharge. Categorical variables were described as counts and percentages and compared using the Chi-square test. Multivariate Cox proportional-hazards regression was used to ascertain whether BNP increase at discharge was an independent predictor of six-month all-cause mortality. The variables used in this model were those that achieved statistical significance at $p < 0.05$ upon univariate analysis or those

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known to be a post-discharge mortality predictor based on prior studies. All statistical tests were performed with a commercially available statistical analysis program (SPSS 15.0 for Windows, SPSS Inc., Chicago, IL, USA). All statistical significance was assessed using a two-sided *p* values. A *p*-value less than 0.05 was considered statistically significant.

Results

Patient characteristics A total of 177 patients (mean age 74 years, 75% males) admitted with ADHF who had their BNP checked on admission and discharge were included in our analysis. Their main clinical, laboratory, anthropometrical and echocardiographic features are represented in Table I. These cases were divided into two groups for comparison based on whether they had BNP increase at discharge relative to admission (no. 53 patients; 29.94%) or not (no. 124 patients;70.06%). There wasn't any significant difference between both groups with regards to admission BNP (423.22 ± 124.286 pg/mL vs. 427.84±123.22 pg/mL, in patients with and without BNP increase at discharge, respectively, p= 0.820)(Table I and Fig 1). Conversely, discharge BNP was significantly higher in patients with BNP rise compared to those without an increase in BNP at discharge (591.47 ± 213.81 pg/mL vs. 170.31 ± 90.10 pg/ mL, respectively; $p < 0.001$).

Table I: Comparison of demographics, clinical, laboratory, and echocardiographic features of patients examined in the retrospective study according to whether or not a patient had BNP rise on discharge relative to admission

	BNP decrease on discharge (no. 124 patients)	**BNP rise on discharge (no. 53 patients)**	**P-value**
Baseline demographics			
Age (years, mean ± SD)	75±13.5	76±14.2	0.6573
Male sex % (n)	72.5%(90)	77.5%(41)	0.5074
BMI on admission (Kg/m^2, mean ± SD)	29.19 ± 6.87	28.68 ± 5.86	0.6350
Comorbidities			
Ischemic etiology of HF % (n)	50.8%(63)	54.7 %(29)	0.7545
Valvular etiology of HF % (n)	7.2%(9)	11.32 %(6)	0.6024
Atrial fibrillation % (n)	29.83%(37)	33.96 %(18)	0.7146
CABG % (n)	25%(31)	35.84%(19)	0.1984
History of hypertension % (n)	69.35%(86)	38(71,69%)	0.8945
DM on insulin % (n)	17.74%(22)	15.09%(8)	0.8327
COPD % (n)	16.12%(20)	18.86%(10)	0.8211
ICD % (n)	13.7%(17)	16.98%(9)	0.7404
NYHA class IV at baseline % (n)	84.67%(105)	90.56(48)	0.4189
Laboratory variables on admission			
Admission BNP (pg/mL, mean ± SD)	427.84±123.22	423.22 ± 124.286	0.820
Discharge BNP (pg/dL, mean ± SD)*	170.31 ± 90.10	591.47 ± 213.81	***p* < 0.001**
Serum creatinine (mg/dL, mean ± SD)	1.46±0.55	1.6±0.4	0.0962
Albumin (g/dL, mean ± SD)	3.70±0.58	3.65±0.56	0.5911
AST (U/L, mean ± SD)	43±22.64	43.80±29.6	0.8451

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Serum Na^+ (meq/L, mean ± SD)	137.5± 10	135.4±8.6	0.1845
Serum K^+ (meq/L, mean ± SD)	4.2±0.65	4±0.85	0.0902
WBC/mm^3 (mean ± SD)	7000±2450	7900 ±4010	0.0692
Hb (g/dL, mean ± SD)	12.5± 2.1	12.1±1.60	0.2164
Echocardiographic data on admission			
LVEF % (mean ± SD)	38.45± 6	37±5.5	0.1331
LVESD (mm, mean ± SD)	59± 10	58±14	0.5916
E/A ratio (mean ± SD)	2.4± 1.25	3.2± 1.35	***p* < 0.001**
Deceleration time (milliseconds, mean ± SD)	142±25	138±22	0.3142

BNP, B-type natriuretic peptide; SD, standard deviation; BMI, body mass index; CABG, coronary artery bypass graft; DM, diabetes mellitus; COPD , chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; AST, aspartate transaminase; Hb, hemoglobin; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; * value recorded on discharge

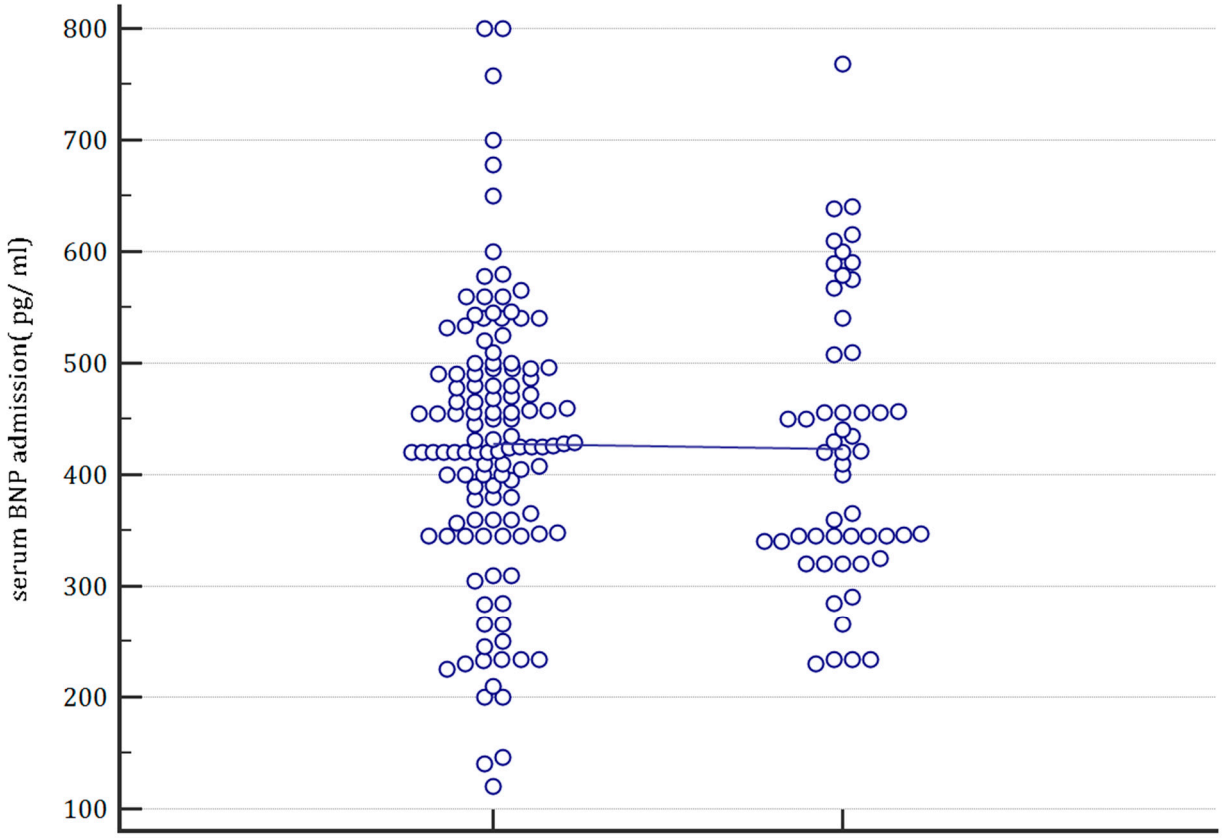

Fig 1

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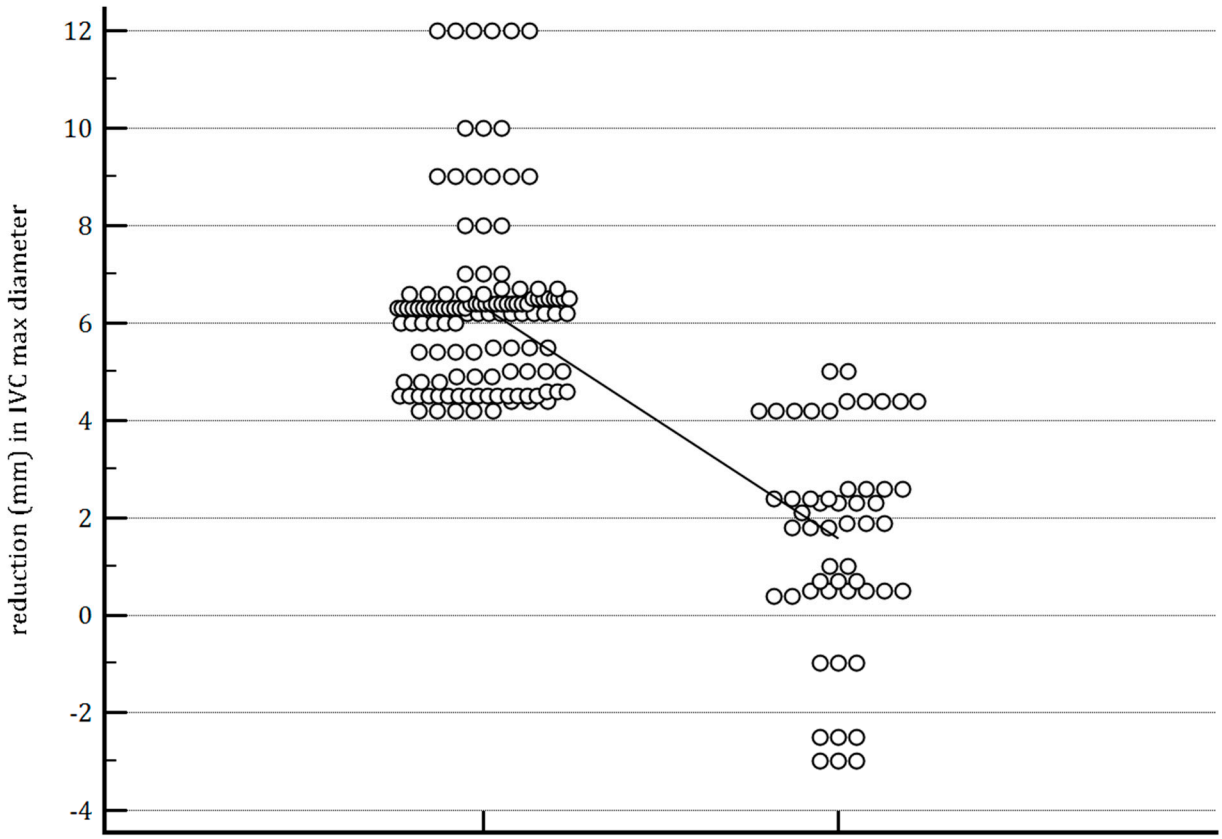

Fig. 2

Clinical and objective markers of congestion By physical exam, patients with BNP increase had higher degree of congestion evident in the higher frequency of patients who had persistence of jugular venous distention at discharge (60.3% vs. 29.03%, odds ratio 3.72, 95% CI 1.8997 to 7.3034; *p*=0.0001) (Table II) as well as persistence of orthopnea at discharge (64.1% vs. 37.9%, odds ratio 2.9317, 95% CI 1.5025 to 5.7203, p=0.0016) (Table III) compared with patients with admission-to-discharge BNP reduction. With regard to objective markers of congestion, patients with BNP increase at the time of discharge had a lower reduction in IVC diameter from admission to discharge (1.58±2.2 mm vs. 6.32±1.82 mm, *p*=0.001) (Fig. 2).By contrast, there wasn't any significant difference in weight loss by comparing patients characterized by BNP increase at discharge with those not involved by BNP rise. Indeed, in the former the weight loss was equal to 2.1308±2.5133 whereas in the latter it was calculated equal to 2.50 ± 1.8921 kg ; *p* (one way ANOVA)= 0.279 .

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	jugular venous distention (jvd)		
	jvd persistence	jvd regression	Total
BNP rising at discharge			
yes	32	21	53
no	36	88	124
Total	68	109	177

odds ratio	3.7249
95% CI	1.8997 to 7.3034
z statistic	3.828
significance level	$p = 0.0001$

Table II . 2 x 2 contingency table showing that in patients hospitalized for acute decompensated heart failure the odds of persistent jugular venous distention is significantly higher among patients with BNP rising at discharge (yes) compared to those free from this laboratory finding (no). For further explanations please see the text.

BNP,B-type natriuretic peptide; jvd,jugular venous distention

	Orthopnea		
	Persistence of orthopnea	Regression of orthopnea	Total
BNP rising at discharge			
yes	34	19	53
no	47	77	124
Total	81	96	177

odds ratio	2.9317
95% CI	1.5025 to 5.7203
z statistic	3.154
Significance level	$p = 0.0016$

Table III . 2 x 2 contingency table showing that in patients hospitalized for acute decompensated heart failure the odds of persistent orthopnea is significantly higher among patients with BNP rising at discharge (yes) compared to those free from this laboratory finding (no). For further explanations please see the text.

BNP,B-type natriuretic peptide

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Six-month mortality A total of 14/177 (7.9%) patients died during a follow-up of 6 months. On multivariate Cox proportional hazards regression patients with BNP increase at discharge were more likely to die (hazard ratio 34.49 95% CI 4.55–261.06; *P* =0.001) compared with those who had BNP decrease at discharge relative to admission. Cox proportional hazard analysis revealed that BNP increase at the time of discharge in patients with previous ADHF was an independent predictor of six-month all-cause mortality after adjustment for age, sodium at discharge, creatinine at discharge and New York Heart Association (NYHA) class at discharge, which are known predictors of post-discharge mortality in HF , based on prior studies (9-10). Figure 3 is a forest plot of variables included in the multivariate model. In our regression model, also serum BNP at admission was included, considering that this factor was regarded as a reliable predictor of all-cause mortality in the mid-term follow-up by other studies (11-12). Nevertheless , in our population of patients with recent episode of ADHF, serum BNP concentration measured at admission was not associated with increased risk of death during a six month follow-up.

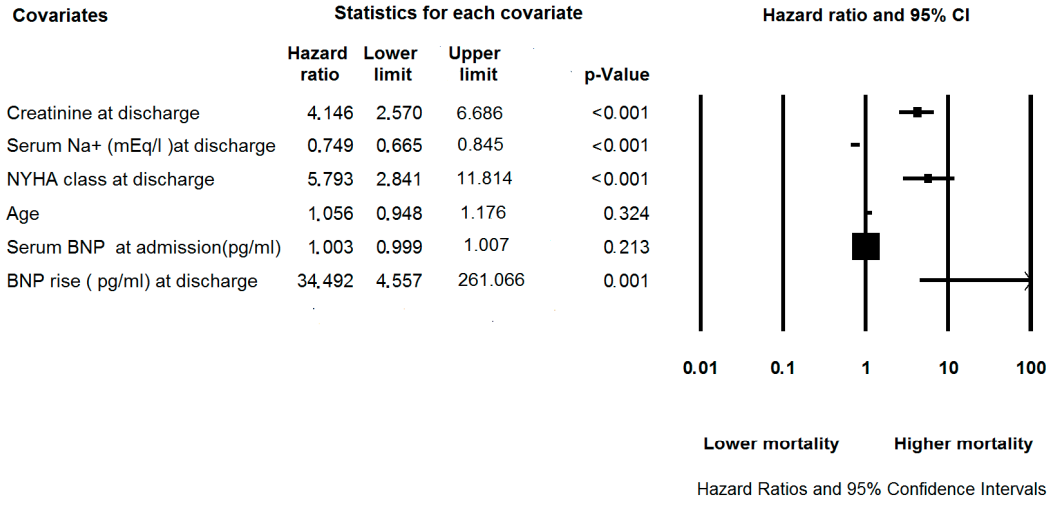

Fig.3 Forest plot showing results of Cox proportional hazard analysis of predictors of 6 month all-cause mortality in our retrospective study that analyzed 177 patients hospitalized for acute decompensated heart failure and undergone clinical follow-up after their hospital discharge.
BNP, B-type natriuretic peptide; NYHA, New York Heart Association

Discussion

Based on our retrospective study, conducted using various tools for statistical analysis (2x2 contingency tables, one-way ANOVA, multivariate Cox proportional hazards regression, etc.), we found that patients with recent acute decompensated heart failure (ADHF) ,who also showed increased serum BNP at discharge, had a grade of decongestion significantly lower, either when clinically identified by observing the regression of jugular venous distention and orthopnea resolution, or when objectively detected through longitudinal, i.e., from admission-to-discharge, assessment of weight loss and reduction in maximum (expiratory) IVC diameter. BNP increase at the time of discharge was also independently associated with six-month mortality after adjustment for known post-discharge mortality predictors in heart failure patients (9-10) including age, discharge creatinine, discharge sodium, and discharge NYHA class. We suspect that the higher mortality in this group may be attributed to the lower grade of decongestion whether due to

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inefficient diuresis, vasodilation and renin–angiotensin–aldosterone system inhibition or, more importantly, due to worse underlying HF pathology, compared with those with admission-to-discharge BNP reduction. Indeed, serum BNP values at admission were not significantly different in the group of HF patients(no. 53), who subsequently developed an increase in BNP at discharge compared to that comprising the HF patients (no. 124), who instead showed decreasing BNP at discharge. Moreover, using multivariate Cox proportional hazards regression, the variable "serum BNP concentration at admission" proved not to be associated to increased risk of death during a six month follow-up.

Thus, judging by our findings, higher all-cause mortality over a six month follow-up in HF patients with BNP increase at the time of discharge suggests that admission-to-discharge BNP change is superior to baseline absolute BNP value in predicting post-discharge outcomes.

The control of BNP secretion is not based solely on mechanisms of hemodynamic signage that come into play when cardiac intra-ventricular pressure exceeds a certain limit (3). Indeed, it is likely that elevated levels of BNP at the time of admission to the hospital may arise from non-hemodynamic factors that have been shown to interfere with the secretion of BNP . For example, a high level of circulating norepinephrine or the coexistence of an altered renal function can affect serum BNP concentrations, pushing them upwards, in addition to the main determinant that is the degree of wall stress of the ventricular chambers(3, 13).

The difficulties related to the interpretation of numerous factors affecting the BNP test limits its role in day-to-day monitoring to guide therapy in acute HF (14). Accordingly, the value of serial BNP measurements in guiding therapy for patients with heart failure is not well established and was not recommended by societal guidelines (15). Nonetheless, our findings still suggest a value for admission and discharge BNP measurements in acute HF, as a BNP increase at discharge is an ominous prognostic factor associated with worse post-discharge outcomes which may have been driven by a higher degree of congestion related to less efficient diuresis or worse HF pathology.

Study limitations The current study is subject to all limitations inherent to non-randomized studies. The design was retrospective. We have not accounted for confounders of BNP level other than the degree of congestion. Thus, there may have been other confounders that have not been accounted for and affected mortality like non-cardiac comorbidities, since the study endpoint was all-cause mortality during a six month follow-up.

Conclusions

BNP increase at the time of discharge relative to admission is not uncommon and indicates a subset of patients with higher grade of congestion and higher six-month mortality compared with those who have admission-to-discharge BNP reduction. Mortality is likely related to less efficient decongestion or, more importantly, it may arise from more severe basal clinical compromise. The fact that this group had higher mortality, despite similar BNP levels at admission, suggests that BNP change from admission to discharge is a discriminating factor more important for prognostic assessment compared to absolute BNP measurement on admission. Longitudinal follow-up of BNP on admission and discharge would therefore be a more reliable measure for predicting post-discharge mortality.

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Figure legends

Fig. 1 In this plot, the admission serum BNP values are categorized depending on the values that they will assume at the hospital discharge(patients with BNP decrease during hospital stay until discharge compared to patients with BNP rising at hospital discharge). Based on these findings, admission serum BNP was not able to predict the subsequent evolution of BNP levels. Indeed, there weren't any differences between basal BNP mean values of patients who will evolve into a BNP decrease at hospital discharge and of those who will show a BNP rise at hospital discharge.

ADHF, acute decompensated heart failure; BNP, B-type natriuretic peptide; pg, pictograms

Fig. 2 The figure shows that patients with BNP increase at the time of discharge had a lower reduction in IVC diameter from admission to discharge (1.58±2.2 mm vs. 6.32±1.82 mm, p=0.001). In the dot-plot, a continuous line connects the means of the two groups(patients with decreasing BNP and the patients whose BNP shows an increase at discharge).

Fig. 3 Forest plot summarizing results of Cox proportional hazard analysis of predictors of six month all-cause mortality in our retrospective study that analyzed 177 patients hospitalized for acute decompensated heart failure and undergone clinical follow-up after their hospital discharge. BNP, B-type natriuretic peptide; NYHA, New York Heart Association