



Article

An Admission-to-Discharge BNP Increase Is a Predictor of Six-Month All-Cause Death in ADHF Patients: Inferences from Multivariate Analysis Including Admission BNP and Various Clinical Measures of Congestion

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Abstract: Background: According to some authors, a single isolated measurement of serum B-type natriuretic peptide (BNP) executed on hospital admission would not be a sufficiently accurate method to predict the outcome of patients with acute decompensated heart failure (ADHF). Aims: To verify 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 increasing BNP at discharge as compared with 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 (30%) had increased BNP at the time of discharge, whereas 124 (70%) showed decreases in serum BNP during their hospital stay. The group with patients who exhibited BNP increases at the time of discharge had a 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 with those with no such increase. A total of 14 patients (7.9%) died during the six-month follow-up period. Multivariable Cox proportional-hazards regression analysis revealed that a BNP increase at the time of discharge was an independent predictor of six-month all-cause mortality after adjustment for persistent jugular venous distention, persistent orthopnea, reduction in inferior vena cava maximum diameter at discharge, weight loss, serum urea, systolic blood pressure at admission, and BNP at admission (hazard ratio = 30.5424; 95% CI: 1.7409–535.8294, $p = 0.0199$). Conclusions: Among patients with a history of ADHF, more elevated BNP levels at the time of discharge from the hospital compared with those detected at admission identify a patient subset with a higher grade of congestion and higher six-month mortality.

Keywords: acute decompensated heart failure; B-type natriuretic peptide; retrospective cohort study; mortality

1. Introduction

Prognostic studies have shown that serum B-type natriuretic peptide (BNP) values, measured after treatment, were more predictive of post-discharge mortality and cardiovascular events, compared with the values recorded at the time of admission [1–4]. Increased BNP in hospital is sometimes detected by comparing values found at admission with those seen at discharge, despite the appropriate treatment of acute decompensated heart failure (ADHF). This denotes a probable greater clinical severity of the underlying heart disease responsible for the recent episode of ADHF requiring hospitalization [5]. However, alternatively, this may suggest that there are other determinants able to come into play to influence the level of serum BNP [6] in addition to the main crucial factor that is the grade of hemodynamic overload of the ventricular myocardium.

2. Aims

In this study, we aimed to detect the six-month all-cause mortality of a number of ADHF patients, all characterized by the fact of having experienced at least one hospitalization for ADHF in the period from January 2012 to January 2015. Subsequently, this cohort was subdivided for study purposes into two subgroups, of which the former consisted of patients who had exhibited a reduction in their serum BNP at the end of hospital stay compared with the admission values, while the latter was composed of patients with increasing BNP at discharge.

Other study objectives included determining the characteristics and grade of congestion of patients with a BNP increase at the time of discharge in comparison with those who had a reduction of discharge BNP.

3. Methods

In the present 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 a confirmed diagnosis of ADHF who belonged to the Division of Cardiology of the Clinic “Sollevio della Sofferenza” of San Giovanni Rotondo (Italy) during the period from January 2012 to January 2015. For inclusion in our retrospective study, the patients were required to have received a diagnosis of ADHF entailing hospitalization. Patients were included in the study if both admission and discharge BNP were measured during the hospital stay. Furthermore, 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 were derived from a 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 [7,8]. In addition, we used two other objective variables, recognized to be suitable to evaluate decongestion [9–11]: weight loss and reduction in the inferior vena cava (IVC) maximum (i.e., expiratory) diameter from admission to discharge. Furthermore, we entered the above-mentioned variables into the multivariate Cox proportional-hazards regression models used for identifying the predictors of six-month all-cause mortality (see Section 3.1).

3.1. Statistical Analysis

Patients with or without a 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 \pm 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. A 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. Univariate and multivariate Cox proportional-hazards regression analyses were used to ascertain whether a BNP increase at discharge was an independent predictor of six-month all-cause mortality. The variables used in these analyses were those known to be a post-discharge mortality predictor based on prior studies [12–14]. Thus, three multivariable Cox regression models were built, using nine exposure variables on the whole: Model 1, including six clinical, echographic, or hematochemical variables (persistent jugular venous distention, persistent orthopnea, reduction in inferior vena cava maximum diameter at discharge, weight loss at discharge, admission systolic blood pressure, serum urea at discharge) plus admission serum BNP (continuous variable); Model 2, with the same explanatory variables used in Model 1 complemented by “BNP increase at discharge relative to admission” (binary variable); Model 3, coinciding with Model 2, except for the adjunct of “BNP at discharge” (continuous variable). 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 two-sided *p*-values. A *p*-value less than 0.05 was considered statistically significant.

4. Results

4.1. 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 1. These cases were divided into two groups for comparison based on whether they had a BNP increase at discharge relative to admission (no. 53 patients; 29.94%) or not (no. 124 patients; 70.06%). There was no significant difference between either group with regard 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 1 and Figure 1). Conversely, discharge BNP was significantly higher in patients with a BNP increase compared with those without an increase in BNPs at discharge (591.47 ± 213.81 pg/mL vs. 170.31 ± 90.10 pg/mL, respectively; $p < 0.001$; Table 1).

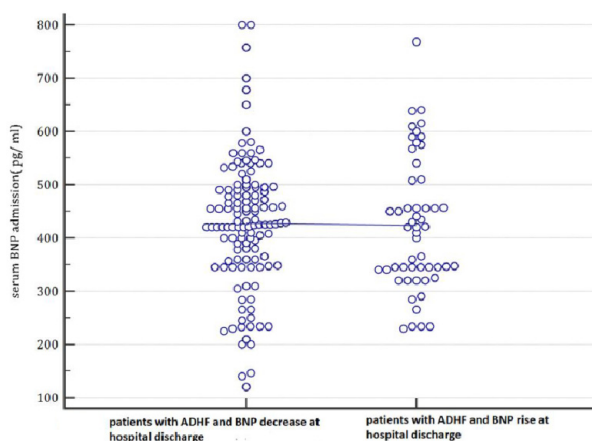


Figure 1. In this plot, the admission serum BNP values are categorized depending on the values that they will assume at the hospital discharge (patients with a BNP decrease during hospital stay until discharge compared to patients with increasing BNP at hospital discharge). Based on these findings, BNP on admission was not able to predict the subsequent evolution of BNP levels. Indeed, there were no differences between the basal BNP mean values of patients who evolve into a BNP decrease at hospital discharge and of those who show a BNP increase at hospital discharge. ADHF: acute decompensated heart failure; BNP: B-type natriuretic peptide; pg: picograms.

Table 1. Comparison of demographics, clinical, laboratory, and echocardiographic features of patients examined in the retrospective study according to whether or not a patient had a BNP rise on discharge relative to admission.

	BNP Decrease on Discharge (no. 124 Patients)	BNP Increase on Discharge (no. 53 Patients)	p-Value
Baseline Demographics			
Age (years, mean \pm SD)	75 \pm 13.5	76 \pm 14.2	0.6573
Male sex % (<i>n</i>)	72.5% (90)	77.5% (41)	0.5074
BMI on admission (Kg/m ² , mean \pm SD)	29.19 \pm 6.87	28.68 \pm 5.86	0.6350
Heart rate on admission (bts/min, mean \pm SD)	99 \pm 19	103 \pm 20	0.2084
Heart rate on discharge (bts/min, mean \pm SD)	64 \pm 18	70 \pm 20	0.0511
SBP on admission (mmHg, mean \pm SD)	165 \pm 26	155 \pm 20	0.0133
SBP on discharge (mmHg, mean \pm SD)	110 \pm 21	107 \pm 18	0.3657
Comorbidities			
Ischemic etiology of HF % (<i>n</i>)	50.8% (63)	54.7% (29)	0.7545
Valvular etiology of HF % (<i>n</i>)	7.2% (9)	11.32% (6)	0.6024
Atrial fibrillation % (<i>n</i>)	29.83% (37)	33.96% (18)	0.7146
CABG % (<i>n</i>)	25% (31)	35.84% (19)	0.1984
History of hypertension % (<i>n</i>)	69.35% (86)	71.69% (38)	0.8645
DM on isulin % (<i>n</i>)	17.74% (22)	15.09% (8)	0.8327
COPD % (<i>n</i>)	16.12% (20)	18.86% (10)	0.8211
ICD % (<i>n</i>)	13.7% (17)	16.98% (9)	0.7404
NYHA class IV at baseline % (<i>n</i>)	84.67% (105)	90.56% (48)	0.4189
Hematochemical Variables			
Admission BNP (pg/mL, mean \pm SD)	427.84 \pm 123.22	423.22 \pm 124.286	0.820
Discharge BNP (pg/dL, mean \pm SD) *	170.31 \pm 90.10	591.47 \pm 213.81	<i>p</i> < 0.001
Serum creatinine (mL/dL, mean \pm SD)	1.46 \pm 0.55	1.6 \pm 0.4	0.0962
Albumin (g/dL, mean \pm SD)	3.70 \pm 0.58	3.65 \pm 0.56	0.5911
AST (U/L, mean \pm SD)	43 \pm 22.64	43.80 \pm 29.6	0.8451
Serum Na ⁺ (meq/L, mean \pm SD)	137.5 \pm 10	135.4 \pm 8.6	0.1845
Serum K ⁺ (meq/L, mean \pm SD)	4.2 \pm 0.65	4 \pm 0.85	0.0902
WBC/mm ³ (mean \pm SD)	7000 \pm 2450	7900 \pm 4010	0.0692
Hb (g/dL, mean \pm SD)	12.5 \pm 2.1	12.1 \pm 1.60	0.2164
Echocardiographic Data on Admission			
LVEF % (mean \pm SD)	38.45 \pm 6	37 \pm 5.5	0.1331
LVEDD (mm, mean \pm SD)	59 \pm 10	58 \pm 14	0.5916
E/A ratio (mean \pm SD)	2.4 \pm 1.25	3.2 \pm 1.35	<i>p</i> < 0.001
Deceleration time (ms, mean \pm SD)	142 \pm 25	138 \pm 22	0.3142

BNP: B-type natriuretic peptide; SD: standard deviation; BMI: body mass index; SBP: systolic blood pressure; 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; LVEDD: left ventricular end-systolic diameter; * value recorded on discharge.

4.2. Clinical and Objective Markers of Congestion

By physical exam, patients with rising BNP levels at discharge had a 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 3.7249, 95% CI 1.8997 to 7.3034; *p* = 0.0001) (Table 2) 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 3), compared with patients with an admission-to-discharge BNP reduction. With regard to objective markers of congestion, patients with a BNP increase at the time of discharge had a lower reduction in IVC diameter from admission to discharge (1.58 \pm 2.2 mm vs. 6.32 \pm 1.82 mm, *p* = 0.001) (Figure 2). By contrast, there was no significant difference in weight loss when comparing patients characterized by a BNP increase at discharge with those not involved in a BNP increase. Indeed, in the former, the weight loss was equal to 2.1308 \pm 2.5133; in the latter, it was calculated equal to 2.50 \pm 1.8921 kg; *p* (one way ANOVA) = 0.279.

Table 2. A 2 × 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 a BNP increase at discharge (yes) compared with those free from this laboratory finding (no). For further explanations, please see the text.

Jugular Venous Distention (jvd)			
	JVD Persistence	JVD Regression	Total
BNP increase at discharge			
yes	32	21	53
no	36	88	124
Total	68	109	177
Odds ratio	3.7249		
95% CI	1.8997–7.3034		
z statistic	3.828		
Significance level	<i>p</i> = 0.0001		

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

Table 3. A 2 × 2 contingency table showing that, in patients hospitalized for acute decompensated heart failure, the odds of persistent orthopnea is significantly higher among patients with a BNP increase at discharge (yes) compared with those free from this laboratory finding (no). For further explanations, please see the text.

Orthopnea			
	Persistence of Orthopnea	Regression of Orthopnea	Total
BNP increase at discharge			
yes	34	19	53
no	47	77	124
Total	81	96	177
Odds ratio	2.9317		
95% CI	1.5025–5.7203		
z statistic	3.154		
Significance level	<i>p</i> = 0.0016		

BNP, B-type natriuretic peptide.

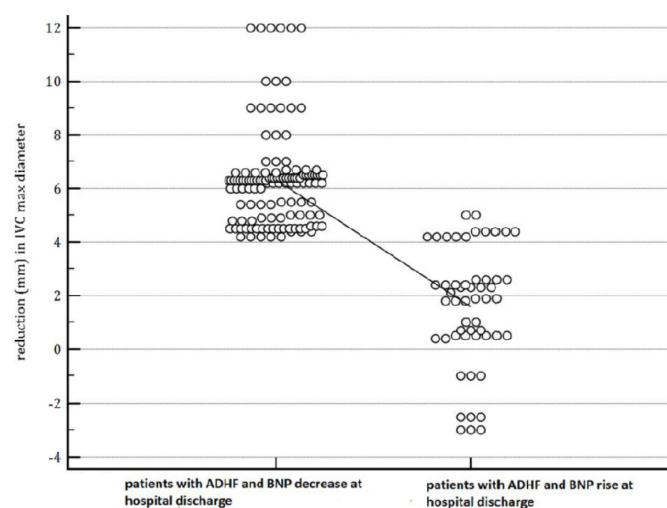


Figure 2. The figure shows that patients with a BNP increase at the time of discharge had a lower reduction in IVC diameter from admission to discharge (1.58 ± 2.2 mm vs. 6.32 ± 1.82 mm, *p* = 0.001). In the dot-plot, a continuous line connects the means of the two groups (patients with decreasing BNP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

4.3. Six-Month Mortality

A total of 14/177 (7.9%) patients died during the six-month follow-up period. The purpose of ascertaining whether the exposure variable “BNP increase at discharge relative to admission” was a reliable predictor of six-month all-cause mortality was achieved by means of the univariate and multivariable Cox regression analyses represented in Tables 4 and 5. Among the three multivariate Cox regression models built in order to evaluate the association of each of the nine exposure variables, overall selected, with the end point “six-month all-cause deaths,” Model 2 (see Table 5) documented that mortality was predicted by “BNP increase at discharge relative to admission” (hazard ratio (HR) = 30.5424; 95% CI: 1.7409–535.8294; $p = 0.0199$). In our regression model, serum BNP at admission was also included, considering that this factor was regarded as a reliable predictor of all-cause mortality in the mid-term follow-up by other studies [15,16]. Nevertheless, in our population of patients with a recent episode of ADHF, serum BNP concentration measured at admission was not associated with an increased risk of death during the six month follow-up. Notably, Model 3 evidenced that “BNP at discharge” was the best predictor of six-month all-cause death (HR = 1.0056; 95% CI: 1.0022–1.0090; $p = 0.0012$).

Table 4. Univariate predictors of six-month all-cause death.

Covariate	Hazard Ratio	95% CI	p-Value
Persistent JVD	1.6666	0.5877–4.7265	0.3393
Persistent Orthopnea	1.2329	0.4347–3.4964	0.6953
Reduction (mm) in IVC max diameter at discharge	0.7791	0.6676–0.9092	0.0016 *
Weight loss at discharge	1.0412	0.8034–1.3495	0.7612
SBP at admission	0.9315	0.9002–0.9638	<0.0001 *
Urea at discharge	1.0526	1.0231–1.0829	0.0004 *
BNP at admission	1.0026	0.9985–1.0067	0.2162
BNP increase at discharge relative to admission	37.7761	4.9906–285.9448	0.0005 *
BNP at discharge	1.0064	1.0046–1.0082	<0.0001 *

Legend: CI: confidence interval; JVD: jugular venous distention; IVC: inferior vena cava; SBP: systolic blood pressure; BNP: B-type natriuretic peptide; * $p < 0.05$.

Table 5. Multivariable predictors of six-month all-cause death.

Model 1 (Seven Covariates)			
Overall Model Fit: Chi-Squared = 49.206; d.f. = 7; Significance Level: $p < 0.0001$			
Covariate	Hazard Ratio	95% CI	p-Value
Persistent JVD	0.5503	0.1567–1.9329	0.3539
Persistent Orthopnea	2.5678	0.6537–10.0868	0.1789
Reduction (mm) in IVC max diameter at discharge	0.7641	0.5904–0.9890	0.0420 *
Weight loss at discharge	1.1080	0.8345–1.4709	0.4806
SBP at admission	0.9374	0.8999–0.9765	0.0020 *
Urea at discharge	1.0629	1.0264–1.1007	0.0007 *
BNPs at admission	1.0011	0.9961–1.0061	0.6710
Model 2 (Eight Covariates)			
Overall Model Fit: Chi-Squared = 56.673; d.f. = 8; Significance Level: $p < 0.0001$			
Covariate	Hazard Ratio	95% CI	p-Value
Persistent JVD	0.4075	0.1150–1.4437	0.1664
Persistent Orthopnea	3.1278	0.6885–14.2091	0.1418
Reduction (mm) in IVC max diameter at discharge	0.9752	0.7117–1.3363	0.8767
Weight loss at discharge	1.1446	0.8548–1.5326	0.3671
SBP at admission	0.9682	0.9278–1.0104	0.1396
Urea at discharge	1.0736	1.0345–1.1142	0.0002 *
BNP at admission	0.9996	0.9947–1.0045	0.8785
BNP increase at discharge relative to admission	30.5424	1.7409–535.8294	0.0199 *

Table 5. Cont.

Model 3 (Nine Covariates)			
Overall Model Fit: Chi-squared = 69.840; d.f. = 9; significance level: $p < 0.0001$			
Covariate	Hazard Ratio	95% CI	p-Value
Persistent JVD	0.1686	0.0381–0.7469	0.0197 *
Persistent Orthopnea	6.1573	0.9606–39.466	0.0564
Reduction (mm) in IVC max diameter at discharge	0.8871	0.6198–1.2717	0.5167
Weight loss at discharge	0.9178	0.6421–1.3118	0.6395
SBP at admission	0.9570	0.9150–1.0009	0.0560
Urea at discharge	1.0509	1.0078–1.0959	1.0209 *
BNP at admission	1.0004	0.9940–1.0069	0.8976
BNP increase at discharge relative to admission	1.4121	0.0502–39.722	0.8402
BNP at discharge	1.0056	1.0022–1.0090	0.0012 *

Legend: CI: confidence interval; d.f.: degree of freedom; JVD: jugular venous distention; IVC: inferior vena cava; SBP: systolic blood pressure; BNP: B-type natriuretic peptide; * $p < 0.05$.

5. Discussion

Based on our retrospective study, we found that patients with recent ADHF, who also showed an increased serum BNP at discharge, had a grade of decongestion that was significantly lower, either when clinically identified by observing the regression of jugular venous distention and orthopnea resolution or when objectively detected through a longitudinal, i.e., from admission-to-discharge, assessment of weight loss and reduction in maximum (expiratory) IVC diameter. Moreover, BNP increase at the time of discharge (binary variable) was independently associated with six-month mortality after adjustment for persistent jugular venous distention, persistent orthopnea, reduction in inferior vena cava maximum diameter at discharge, weight loss, serum urea, systolic blood pressure at admission, and BNP at admission (see Table 5, Model 2). Furthermore, in Cox Model 3 (Table 5), BNP at discharge (continuous variable) proved to be the strongest predictor of six-month all-cause death ($p = 0.0012$), so as to obscure the predictive value exhibited by “BNP increase at discharge relative to admission.” Therefore, in ADHF patients, for whom one wants to make a prognosis about the risk of death at six months, reference predictors should be “BNP measured at discharge” (continuous variable) or even “increasing BNP on discharge” (dichotomous variable).

We suspect that the higher mortality in the group with increasing BNP at discharge may be attributed to the lower grade of decongestion whether due to inefficient diuresis, vasodilation, and renin–angiotensin–aldosterone system inhibition or, more importantly, due to worse underlying HF pathology, compared with those with an 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 of the HF patients (no. 124), who instead showed decreasing BNP at discharge. Moreover, using multivariate Cox proportional hazards regression, the variable “serum BNP at admission” proved not to be associated to increased risk of death during the 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 the 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 [6]. 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, the degree of wall stress of the ventricular chambers [6,17].

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 [18]. 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 [19]. 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 that 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. We did not evaluate the medical therapy during the hospital stay. Therefore, a lack of adequate medical therapy may have been responsible for the increase in serum BNP found at discharge in some patients.

6. Conclusions

A 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; alternatively, and more importantly, it may arise from a more severe basal clinical compromise. The fact that this group had higher six-month 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. Based on this study, in ADHF patients, a longitudinal follow-up of BNP on admission and discharge would therefore be a more reliable measure for predicting post-discharge mortality with respect to admission BNP levels.

Author Contributions: The authors declare that they participated equally in the conception and design of the research as well as in the analysis and interpretation of the collected data. Likewise, all authors participated equally in the writing of the article as well as in its critical revision.

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