

Prognostic Value of Brain Natriuretic Peptide in Acute Heart Failure: Mortality and Hospital Readmission

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The prognostic value of brain natriuretic peptide (BNP) measurement in patients with acute heart failure is not well understood. The aim of this study was to investigate the relationship between the BNP level and mortality and readmission for acute heart failure. We studied 569 consecutive patients who were admitted with a diagnosis of acute heart failure. The BNP level was measured after the patient became clinically stable. The relationship between the BNP level and mortality was assessed by Cox regression analysis, and the relationship with readmission, by competing risks regression analysis. During a median follow-up period of 9 (range, 3-18) months, 156 deaths (27.4%) and 140 readmissions (24.6%) occurred. Multivariate analysis demonstrated a positive linear association between the risk of death and the BNP quintile. In contrast, the BNP level did not predict readmission for acute heart failure, mainly because of the effect of death as a competing outcome.

Key words: Acute heart failure. Brain natriuretic peptide. Prognosis.

Implicaciones pronósticas del péptido natriurético cerebral en la insuficiencia cardiaca aguda: mortalidad y reingresos hospitalarios

El valor pronóstico del péptido natriurético cerebral (BNP) tras un episodio de insuficiencia cardiaca aguda (ICA) no ha sido totalmente establecido. El objetivo de este trabajo fue evaluar la relación entre las concentraciones de BNP y la mortalidad y los reingresos por ICA. Analizamos a 569 pacientes ingresados consecutivamente con el diagnóstico de ICA. Se determinó el BNP tras la estabilización inicial del paciente. La relación entre el BNP y la mortalidad fue evaluada mediante regresión de Cox y la relación con el reingreso, mediante regresión con ajuste para episodios competitivos. Durante una mediana de seguimiento de 9 (3-18) meses, se registraron 156 muertes (27,4%) y 140 reingresos (24,6%). En el análisis multivariable se observó una asociación positiva y lineal entre el riesgo de mortalidad y los quintiles de BNP. Para reingreso por ICA, el BNP no mostró tener valor predictivo debido al efecto de la mortalidad como episodio competitivo.

Palabras clave: Insuficiencia cardiaca aguda. Péptido natriurético cerebral. Pronóstico.

INTRODUCTION

Numerous studies support the use of brain natriuretic peptide, also known as B-type natriuretic peptide (BNP), as a risk marker in various cardiovascular conditions; however, the predictive value attributable to BNP in an

unselected population admitted for acute heart failure (AHF) remains uncertain, and its influence on intermediate episodes, such as new hospital readmissions assessed independently (not as part of a combined event), has still not been described. The aim of our study was to assess the relationship between BNP, measured during the AHF episode, and mortality and hospital readmission for AHF, adjusting for mortality as a competing event.

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METHODS

Study Group and Protocol

We prospectively included 569 patients admitted to the cardiology department of our hospital with a diagnosis

of AHF between June 1, 2004 and December 31, 2006. The diagnosis was established by cardiologists in accordance with the current recommendations.¹ Patients with acute coronary syndrome, active neoplastic or infectious disease, or end-stage renal disease on dialysis were excluded from the study, as were patients who were initially admitted with AHF but whose main reason for admission was considered to be other than AHF (n=32). The patients were individually managed, following current recommendations.¹ During admission, a single observer performed the transthoracic echocardiography. BNP (as measured by the ADVIA Centaur immunoassay system) was determined within a median of 48 hours (range, 42-54 h) after hospital admission and always after the first 24 hours.

Statistical Analysis

Continuous variables were expressed as mean (SD) or median (interquartile range) as appropriate, and discrete variables as percentages. The baseline characteristics of the population were stratified by BNP distribution quintile. Analysis of variance was used to compare continuous variables with normal distribution; otherwise, the Kruskal-Wallis test was used. For discrete variables, the χ^2 test was used. The linear trend of proportions was also analyzed using the linear trend test. The percentage of deaths in each BNP category was estimated by Kaplan-Meier curves, and the differences were quantitated by the log-rank test. The adjusted proportion of readmissions for AHF was estimated by cumulative incidence, and the differences between BNP quintiles were quantitated by the Gray test.² To assess the intrinsic effect of BNP on the hospital readmission rate, contingent on whether the patient was living during follow-up, the conditional probability method of Pepe et al³ was used. The Cox regression model was used to analyze the association between BNP and mortality, whereas the regression model of Fine et al⁴ and Gray² was used for competing risks of readmission due to AHF. In both cases, or if the variable presented $P < .2$ in the univariate analysis, variables of recognized prognostic value in the medical literature were included. Once the initial models had been established, they were simplified by stepdown elimination. The estimated coefficients were expressed as the hazard ratio (HR) with the respective 95% confidence intervals (CI). The final discriminatory ability of the multivariate models was determined by Harrell's C statistic. A P value less than .05 was considered significant in all cases. The STATA 9.2 and R (cmprsk) statistical packages were used for the statistical analyses.

RESULTS

Sample Characteristics Stratified by BNP Level

The mean age (SD) of our population was 73.8 (10.6) years; 52.4% were women. The mean (SD) and the median

BNP level were 311 (425) and 152 (interquartile range, 90-356) pg/mL, respectively. In general, a positive, monotonic association was observed between the most common AHF severity parameters and the BNP quintiles (Table 1).

Relationship of BNP With Mortality

During a median follow-up of 9 (interquartile range, 3-18) months, 156 (27.4%) deaths were recorded, 24 for the index hospitalization and 132 after hospital discharge. The mortality distribution stratified according to BNP quintile showed a monotonic increase from lowest to highest BNP quintile (6.1%, 20.2%, 26.3%, 29.8%, and 54.9%; trend, $P < .001$) (Figure 1). In the final multivariate analysis, BNP was positively and closely associated with mortality (Table 2). We did not include variables such as left ventricular ejection fraction, type of AHF, or ischemic etiology in the final model, due to the absence of statistical association with mortality. Additionally, no significant interactions were found between BNP levels and potential confounding variables such as left ventricular systolic function, etiology of heart failure, kidney function, or gender. The Harrell's C statistic was higher in the model that included BNP compared to the same model without this value (0.801 vs 0.781).

Relationship of BNP With Hospital Readmissions for AHF

During follow-up, 140 (24.6%) hospital readmissions for AHF were recorded. The percentages of readmissions corresponding to the BNP quintiles were, from lowest to highest, 21.1%, 21.9%, 22.8%, 26.3%, and 31% (trend, $P = .058$). Figure 2 shows the curve of hospital readmissions, stratified by BNP quintile or by $\text{BNP} \geq 100$ pg/mL. BNP did not show a significant effect in either case (Gray test, $P = .79$ and $P = .44$, respectively). To estimate the theoretical effect that BNP might have on the hospital readmission rate for AHF in the ideal context where mortality as a competing event could be eliminated, we decided to use the conditioned probability model.⁴ Figure 3 shows a significant separation between dichotomized BNP levels (≥ 100 pg/mL), which confirmed its innate predictive value for readmission due to AHF, even though the high simultaneous mortality rate in our population masked this property.

DISCUSSION

In this study on a consecutive population of patients admitted with a diagnosis of AHF, we found a positive, strong, and independent association between BNP levels (measured during the first few days of hospitalization) and mortality. In addition, the analysis of intermediate events, examined with the use of innovative methodology, showed that BNP levels were not associated with a risk

TABLE 1. Baseline Sample Characteristics, Stratified By BNP Quintile

Variables	BNP, pg/mL					P
	Q1 (20-85) (n=114)	Q2 (85-123) (n=114)	Q3 (123-250) (n=114)	Q4 (251-490) (n=113)	Q5 (495-3.240) (n=113)	
Demographic and medical history						
Age, mean (SD), y	71 (12)	73 (10)	74 (10)	73 (12)	77 (9)	<.001
Women, %	55.3	60.5	51.8	50	44.2	.028
Hypertension, %	74.6	78.9	83.3	82.5	76.1	.581
Dyslipidemia, %	47.4	35.1	36	33.3	26.6	.002
Active smokers, %	10.5	7.9	7.9	12.4	8.9	.897
Diabetes mellitus, %	45.6	36.8	41.2	43	37.2	.462
Ischemic heart disease, %	27.2	31.6	38.6	39.5	52.2	<.001
Valvular heart disease, %	22.8	30.7	30.7	20.2	23.9	.520
Prior admissions for AHF, %	28.1	36	34.2	49.1	53.1	<.001
Decompensated AHF, %	61.4	71.9	73.7	67.5	65.5	.782
Acute pulmonary edema, %	26.3	15.8	18.4	20.4	25.6	.804
Hypertensive AHF, %	10.5	10.5	7.9	9.6	5.3	.179
NYHA class III/IV (baseline), %	16.7	16.7	23.7	15.8	30.1	.031
COPD, %	18.4	17.5	21.9	19.3	23	.358
Charlson index \geq 2, %	24.6	34.2	35.1	39.5	53.1	<.001
Pleural effusion, on radiologic imaging, %	38.6	45.6	46.5	53.5	55.7	.004
Peripheral edema, %	43	62.3	57	59.6	65.5	.004
Prior treatment with diuretics, %	52.6	67.5	64	71	77.9	<.001
Prior treatment with ACE inhibitors/ARBs, %	43.8	46.5	47.4	49.1	47.8	.478
Prior treatment with beta-blockers, %	24.5	18.4	25.4	21.9	21.2	.800
Vital signs						
Heart rate, bpm	100 [40]	95 [40]	102 [47]	100 [37]	90 [36]	.134
Systolic blood pressure, mm Hg	160 [65]	140 [40]	140 [44]	140 [58]	140 [40]	<.001
Diastolic blood pressure, mm Hg	90 [30]	80 [30]	80 [22]	80 [20]	80 [20]	.001
ECG						
Atrial fibrillation, %	46.5	52.6	50.9	36.8	34.5	.007
QRS >120 ms, %	25	34.9	27	37.7	46.4	.001
Laboratory workup						
Hemoglobin, g/dL	13 (1.9)	12.8 (1.9)	12.9 (1.7)	12.9 (1.9)	12.3 (2.1)	.021
Leukocytes, cells/ μ L	10.6 (4)	9.6 (3.2)	10.2 (3.2)	10.2 (3.6)	10.3 (4.5)	.620
Serum creatinine, mg/dL	1.1 [0.4]	1.2 [0.4]	1.3 [0.6]	1.4 [0.6]	1.6 [0.6]	<.001
Uric acid, mg/dL	7.7 (2.3)	7.7 (2.8)	7.9 (2.3)	7.6 (2.1)	8.5 (2.5)	.032
Sodium, mEq/L	139 (4)	139 (4)	139 (4)	138 (5)	139 (6)	.251
Troponin I >0.2 ng/mL, %	26.3	23.7	28.1	29.8	39.8	.015
Echocardiography						
LVEF \leq 45%	23.7	27.2	39.5	47.4	57.5	<.001
LAD, mm	43 (7)	45 (9)	43 (6)	44 (6)	45 (7)	.121
LVEDD, mm	53 (9)	54 (10)	56 (9)	58 (11)	59 (9)	<.001
Treatment						
Diuretics, %	98.3	98.3	99.1	99.1	99.1	.424
ACE inhibitors, %	43.9	35.1	44.7	42.1	33.6	.357
Beta-blockers, %	49.1	47.4	60.5	57.9	41.6	.768
ARBs, %	27.2	32.5	28.1	30.7	27.4	.926
Digital, %	28.9	35.1	21.1	32.5	26.6	.581
Spirolactone, %	12.3	18.4	15.8	14.9	12.4	.757
Anticoagulants, %	43	43	42.1	31.6	25.7	.001
Antiplatelet agents, %	28.1	33.3	37.7	42.1	47.8	.001
Nitrates, %	15.9	15	20.3	25.4	34.2	<.001

ACEIs indicates angiotensin-converting enzyme inhibitors; AHF, acute heart failure; ARBs, angiotensin-receptor antagonists II; COPD, chronic obstructive pulmonary disease; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction.

Continuous variables are expressed as mean (SD) or median [interquartile range]; categorical variables are expressed as percentages.

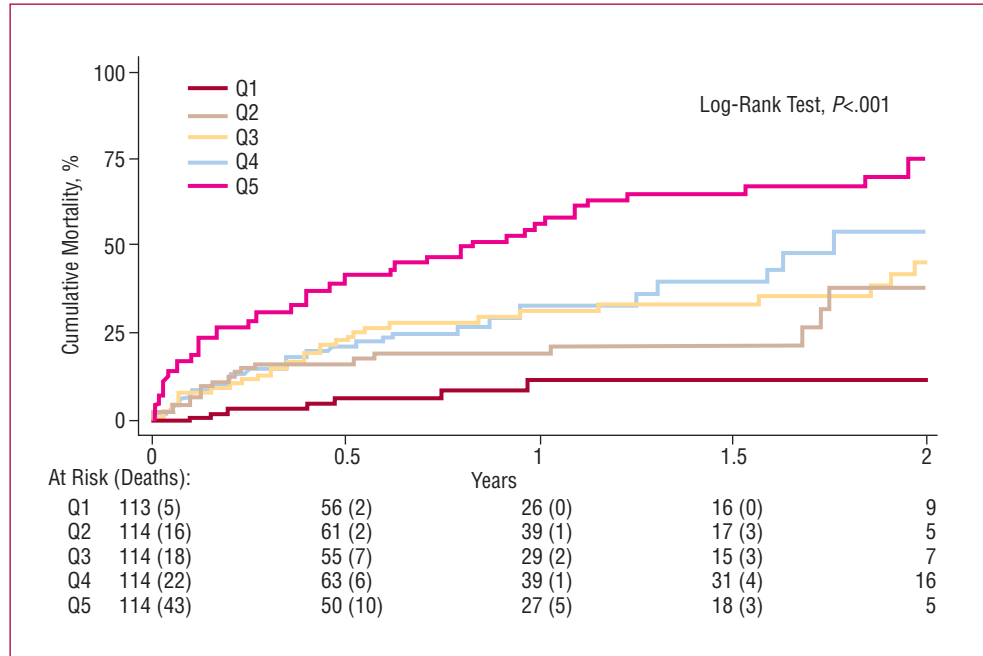


Figure 1. All-cause mortality during follow-up, stratified by BNP quintile. The number of patients at risk and the number of deaths that have occurred are specified at each follow-up point. BNP indicates brain natriuretic peptide.

TABLE 2. Hazard Ratio for Total Mortality According to BNP Level

Cox Regression Models	HR (95% CI)	P	Harrell C
Nonadjusted HR			
BNP by increments of 100 pg/mL ^a	1.07 (1.05-1.1)	<.001	0.663
BNP quintiles, pg/mL (minimum-maximum)			0.661
Q1 (20-85)	1		
Q2 (85-123)	3.1 (1.33-7.24)	.009	
Q3 (123-250)	4.35 (1.91-9.92)	<.001	
Q4 (251-490)	4.01 (1.78-9.06)	.001	
Q5 (495-3240)	9.37 (4.29-20.47)	<.001	
Adjusted HR^b			
BNP by increments of 100 pg/mL	1.05 (1.03-1.08)		0.798
BNP quintiles, pg/mL (minimum-maximum)			0.801
Q1 (20-85)	1		
Q2 (85-123)	2.75 (1.17-6.46)	.02	
Q3 (123-250)	2.76 (1.20-6.33)	.016	
Q4 (251-490)	3.38 (1.49-7.68)	.004	
Q5 (495-3240)	5.82 (2.62-12.97)	<.001	

BNP indicates brain natriuretic peptide; HR, hazards ratio.

^aArea under the ROC curve =0.718.

^bFinal Cox model adjusted for age, valvular etiology, baseline NYHA functional class, prior admissions for acute heart failure, prior treatment with beta-blockers, systolic blood pressure, serum creatinine, and hemoglobin.

of hospital readmission due to AHF; however, this finding was influenced by the high mortality rate of our population, which prevented BNP from showing its biological value as a predictive factor for readmissions.

Optimal Time Point for BNP Measurements

Because BNP has a short half-life (15-20 min), the variation observed in baseline values following the

administration of aggressive treatment is substantial. This fact, rather than a problem, has been used as a clinical tool to assess therapeutic response; thus, most studies that analyze the prognostic value of BNP or NT-proBNP after an AHF event report that serial or pre-hospital discharge measurements are prognostically superior to measurements taken at admission. However, this approach limits in-hospital prognostic stratification and BNP cannot be used as a therapeutic guide, as several other studies

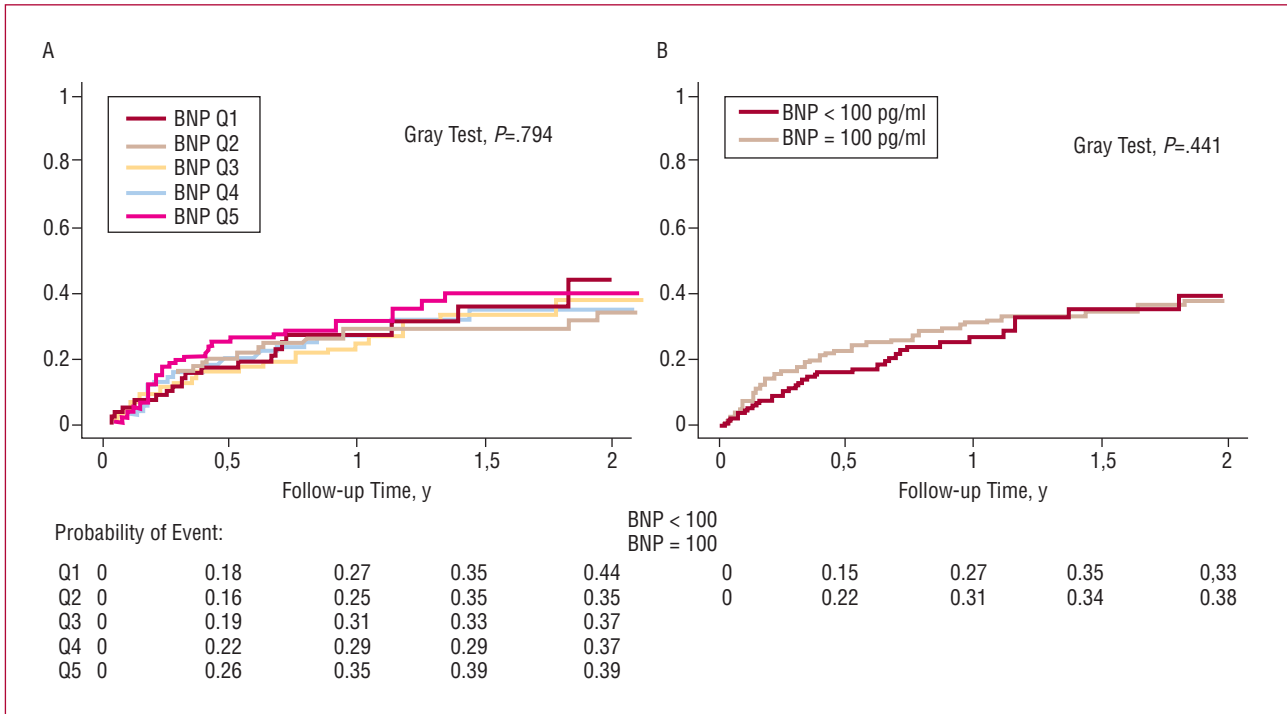


Figure 2. A: cumulative incidence of readmissions, stratified by BNP quintiles. B: cumulative incidence of readmissions stratified by BNP level, dichotomized according to ≥ 100 pg/mL and < 100 pg/mL. Both cases were adjusted for mortality during follow-up as a competing event. Abbreviations: BNP, brain natriuretic peptide.

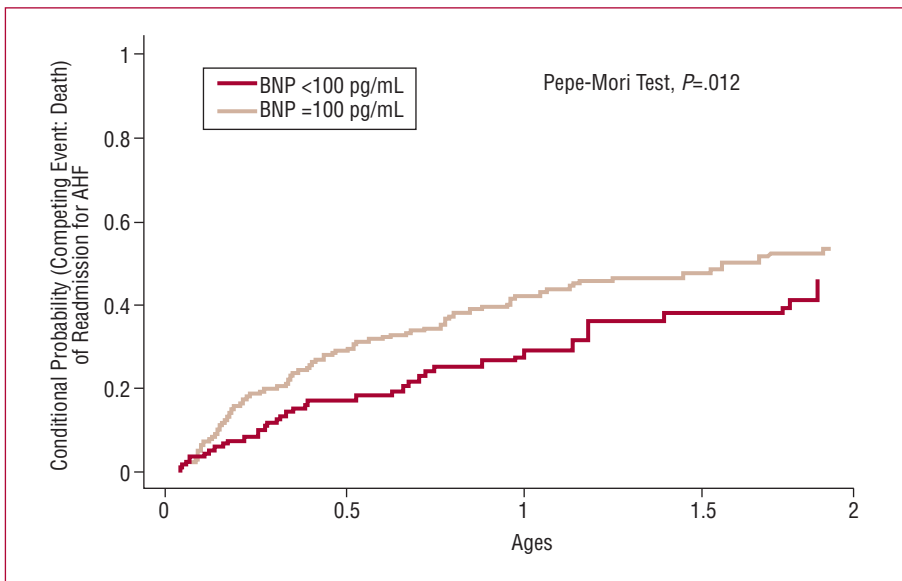


Figure 3. Conditional probability of readmission for acute heart failure (AHF), eliminating death as a competing event, stratified by BNP level into ≥ 100 pg/mL and < 100 pg/mL. BNP indicates brain natriuretic peptide.

have indicated. Our approach, which consisted of measuring BNP after initial clinical stabilization, provides a biologically feasible strategy, integrating information from BNP levels at admission and its theoretical response after initial aggressive treatment, making it possible to perform risk stratification earlier than when BNP is measured before hospital discharge.

BNP and Hospital Readmissions for AHF

BNP, in any of its presentations, showed no predictive value for readmission due to AHF (Figure 2). However, the conditional probability analysis confirmed that, under ideal and theoretical circumstances in which mortality could be eliminated, BNP has significant predictive effect for hospital readmission due to AHF (Figure 3).

Limitations

This study has certain limitations. First, its observational nature may have introduced bias related to the difficulty for including prognostic variables that are unknown or not collected in our records. Second, although BNP was usually measured early in the hospitalization, it was not done in all patients at the same time point after admission, a fact that introduces some variability. Lastly, owing to the absence of serial measurements, we cannot establish the time point offering the greatest prognostic yield in this situation.

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