

B-type natriuretic peptide predicts long-term prognosis in a cohort of critically ill patients

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Abstract

B-type natriuretic peptide is an important prognostic marker in heart failure. However, there are limited data for its value in non-cardiac intensive care unit patients, namely regarding long-term prognosis. We investigated the long-term prognostic value of BNP in a cohort of critically ill patients. This was a

prospective and observational study, conducted in a tertiary university hospital 20-bed intensive care unit. We included 103 mechanically-ventilated patients admitted for a non-cardiac primary diagnosis; B-type natriuretic peptide samples were obtained on admission. A mean 14 (3-30) month follow up was available in 96.1% of patients who were discharged from hospital. Mean age was 60.7±19.0 years and mean APACHE II score was 16.2±7.2. APACHE II score and renal dysfunction increased with rising B-type natriuretic peptide, with more than 60% of patients having B-type natriuretic peptide levels of 100 pg/mL or over; echocardiography-derived left ventricular ejection fraction was lower in patients with higher B-type natriuretic peptide ($P < 0.001$). Long-term survivors had lower median B-type natriuretic peptide values (117.5 [2-1668] pg/mL) compared with intensive care unit non-survivors (191.0 [5-4945] pg/mL), $P < 0.001$. After adjustment to APACHE II score, B-type natriuretic peptide levels of 300 pg/mL or over were independently associated with long-term mortality (odds-ratio 4.1 [95% CI 1.45-11.5], $P = 0.008$). We conclude that in an unselected cohort of intensive care unit patients, admission B-type natriuretic peptide is frequently elevated, even without clinically apparent acute heart disease, and is a strong independent predictor of long-term mortality.

of dyspnea and is recommended as a screening tool in the latest heart failure (HF) guidelines.² BNP is also an independent predictor of cardiovascular events after an HF diagnosis, either acutely decompensated³ or in stable subjects.⁴ The mortality risk is proportional to the magnitude of the BNP level on admission, with an increase of the relative risk of death of 35% for every 100 pg/mL.⁵ Although the prognostic value of BNP is well established in patients with HF, acute coronary syndromes (ACS)⁵ and acute pulmonary embolism,⁶ its role in the non-cardiac critically ill patient is still under close scrutiny.⁷ Indeed, there are no data regarding its capability of predicting long-term prognosis in this subset of patients. We, therefore, studied the long-term prognostic impact of BNP in an unselected cohort of non-cardiac patients admitted to an intensive care unit (ICU) of a tertiary care hospital.

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Materials and Methods

Study protocol and patient population

We conducted a prospective, single-center, observational study at the Department of Intensive Care Medicine of the Coimbra University Hospital between September 2007 and December 2007. Our unit is a 20-bed tertiary care polyvalent medical and surgical ICU that treats the entire spectrum of medical, surgical and trauma patients. Adult patients were eligible if they did not have an acute decompensated cardiac condition (ACS and acute pulmonary embolism as defined by current guidelines,^{2,8,9} acute decompensated HF or acute arrhythmias as judged by the physician responsible), as these patients are usually admitted by the cardiology department in a dedicated 20-bed ICU. Patients with preexisting coronary artery disease (CAD), history of congestive HF and chronic supra-ventricular arrhythmias, such as atrial fibrillation, were included. If a patient required multiple admissions to the ICU, data was collected only dur-

Introduction

B-type natriuretic peptide (BNP) is a 32 amino-acid neurohormone released by the ventricles, secondary to the stretch of the cardiac myocytes. It has powerful physiological effects on other organs, including the kidney and vasculature, as it modulates myocardial stretch and plasma volume through its diverse actions as a diuretic, renin-angiotensin-aldosterone system antagonist, vasodilator and inhibitor of sympathetic nerve activity.¹ In the emergency room (ER) or in the outpatient setting, an increased plasma BNP level can help to distinguish cardiac and non-cardiac causes

ing the initial admission. Sepsis was defined by the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee.¹⁰ The study was conducted in accordance with applicable laws and regulations, and ethical principles that have their origin in the Declaration of Helsinki. The study protocol was approved by the Coimbra University. The hospital review board and patients gave their informed consent for the data to be used in the analysis.

Blood sampling

For each patient, in addition to admission routine laboratory assessment, BNP was determined using a commercially available assay (ADVIA Centaur® CP, Siemens, Germany). Blood in EDTA was immediately transported to our hospital central laboratory where it was processed and analyzed within one hour. The cut-off values for diagnosis of decompensated HF have been established elsewhere (BNP ≥ 100 pg/mL).²

Data collection

Baseline demographics and clinical history were recorded in all patients. According to the primary diagnosis on admission to the ICU, the reason for admission was classified as medical, surgical or trauma. *Medical* was defined as a primary medical diagnosis (e.g. pneumonia). Medical did not preclude a secondary cardiac disease, nor was a preexisting cardiac disease a priori excluded. *Surgical* was defined in patients that had been subjected to a surgical procedure which was the reason for hospital admission. *Trauma* patients were defined as patients admitted due to a trauma. Disease severity was scored according to the Acute Physiology and Chronic Health Evaluation (APACHE II) system using available data from the 24 h period at the time of enrolment, with higher values indicating more severe illness.¹¹ Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula.¹² On the basis of the BNP value on admission, we divided the population into two pre-specified groups of more than 300 pg/mL⁻¹ or less than 300 pg/mL⁻¹, according to literature data.¹³⁻¹⁵

Echocardiographic sub-study

An echocardiogram was performed within the first 24 h of admission by the same experienced dedicated intensivist operator, the examination being ordered at the discretion of the primary medical team, if clinically advised. Echocardiography was obtained in 43 patients using a Toshiba® (Nemio 30, Tokyo, Japan) sonographer with a 2.5 MHz probe. Measurements were made in M mode and left ventricular ejection fraction was calculated by

biplanar Simpson's method. Pulmonary artery pressure was assessed by the measurement of peak tricuspid regurgitation velocity by continuous Doppler plus estimated right atrial pressure from inferior vena cava measurements.

Study outcomes

ICU survival and hospital survival were recorded in all patients, whereas long-term survival (median 14 (3-30) months) was available in 96.1% of patients (99/103). Follow up was obtained by personal or telephonic interview and review of medical charts.

Statistics

Continuous variables are expressed as mean \pm SD or median and range if the assumption of a normal distribution was violated, using the Kolmogorov-Smirnov test. Categorical variables are given as percent. Comparisons of parameters between two groups were made by unpaired Student's t-test or the Mann-Whitney U test, as appropriate. APACHE II and BNP were evaluated for their independent association with long-term survival by logistic regression. Correlation between BNP values and echocardiographic variables and between BNP and APACHE II score were performed by bivariate analyses with Spearman's correlation. Survival was analyzed by the Kaplan-Meier method. SPSS 12.0.1 (SPSS, Chicago, IL, USA) was used for statistical analyses. $P < 0.05$ was considered significant in all analyses.

Results

Patients' characteristics

We enrolled 103 patients in the study, with a mean age of 60.7 ± 19.0 years, of whom 60.2% were male. All patients required mechanical ventilation, and the mean FiO₂ was $57 \pm 18\%$. There was a wide range of disease severity, with a mean APACHE II score of 16.2 ± 7.2 . Mean BNP serum concentrations were markedly elevated (mean: 462.9 pg/mL⁻¹; median: 159 pg/mL⁻¹) over a broad range ($2-4945$ pg/mL⁻¹). Only 39.8% (41 of 103) of the patients had values on admission low enough to exclude decompensated HF as per current guidelines (< 100 pg/mL⁻¹) and almost one-third of the patients (31.1%) had a BNP of 300 pg/mL⁻¹ or over. Most patients were admitted for a medical illness (52.0%), followed by surgical and trauma in similar proportions (24.0%). Of the patients admitted for medical illness, the most common diagnosis was pneumonia (48.1%). Most trauma patients had head trauma (62.5%). The most common diagnosis in surgical patients was post-operative sepsis (64.0%). BNP levels

were significantly lower in trauma patients (39 [$13.5-145.3$] pg/mL⁻¹), compared with medical (188.5 [$69.8-464.0$] pg/mL⁻¹) and surgical patients (195.0 [$75.5-566.3$] pg/mL⁻¹), $P = 0.003$.

Outcomes

There were 74 ICU survivors and 29 ICU non-survivors (28.2%). A total of 62 patients survived to discharge from hospital and 39.8% died before discharge. At a median follow up of 14 (3-30) months, there were 42 (42.4%) survivors and 57 non-survivors (57.6%).

BNP and clinical data

We divided BNP values into two groups (< 300 pg/mL⁻¹ and ≥ 300 pg/mL⁻¹) to compare clinical (Table 1) and laboratory characteristics (Table 2). BNP was higher in older patients ($P < 0.001$), with increasing APACHE II scores and organ failure. As expected, patients with higher BNP had a higher prevalence of prior CAD, HF and hypertension. Estimated GFR levels were lower in the group with BNP 300 pg/mL⁻¹ or over whereas CVP levels were increased, as were supportive interventions, including vasopressor usage. Troponin I was significantly higher in patients with higher BNP levels (Table 2). Disease severity translated by the APACHE II score, correlated well with BNP ($P = 0.020$, $r = 0.228$).

BNP and echocardiographic data

Echocardiographic data was available in 43 patients, collected within the first 24 h of admission by the same experienced operator. BNP showed good correlation with left ventricular ejection fraction (LVEF) ($r = 0.403$, $P = 0.007$), but no correlations were found with other parameters (Table 3).

BNP on admission and outcomes

Patients with a BNP of 300 pg/mL⁻¹ or over had a long-term mortality rate of 80%, compared with 48% in the group of patients with BNP less than 300 pg/mL⁻¹, yielding a hazard-ratio of 2.25 (1.3-3.8) (log rank test $P = 0.045$) (Figure 1). Regarding long-term follow up, survivors had lower admission BNP values (median 117.5 [range $2-1668$] pg/mL⁻¹) than non-survivors (191.0 [$5-4945$] pg/mL⁻¹), $P = 0.013$. ICU survivors had significantly lower BNP values (BNP 117.5 [$2-4875$] pg/mL⁻¹) than ICU non-survivors (328 [$27-4945$] pg/mL⁻¹), $P = 0.003$. Likewise, hospital survivors were characterized by significantly lower BNP values (125 [$2-4875$] pg/mL⁻¹) vs non-survivors (194 [$18-4945$] pg/mL⁻¹), $P = 0.031$. In a logistic multivariable regression model, values of BNP over 300 pg/mL⁻¹ were independently associated with long-term mortality (OR 4.1 [95% CI 1.45-11.5], $P = 0.008$), even

after adjustment to APACHE II score. Discrimination was moderately better when BNP was added to the APACHE II score, regarding long-term survival (c-statistic = 0.727 [95% CI 0.628-0.812] vs 0.666 [95% CI 0.560-0.754], P=0.114) (Figure 2). Using the European HF guidelines cut-off of 400 pg/mL⁻¹ for decompensated HF², the results regarding long-term prognostic ability and predictive power after adjustment to APACHE II score are similar.

Table 1. Patients' baseline characteristics.

n = 103 patients	Total	BNP <300 pg/mL ⁻¹	BNP ≥300 p/mL ⁻¹	P value
Demographics				
Age (years) (mean, SD)	60.7±19.0	56.1±19.0	69.4±16.3	0.001
Male (%)	60.2	62.0	56.3	0.583
Prior history				
Coronary heart disease (%)	7.4	1.9	18.5	0.007
Stroke/TIA (%)	13.4	14.4	11.1	0.668
Peripheral artery disease (%)	7.3	5.5	11.1	0.355
Arterial hypertension (%)	52.5	43.4	70.4	0.022
Diabetes mellitus (%)	15.0	18.9	7.4	0.175
Congestive heart failure (%)	33.0	22.1	56.3	0.001
COPD (%)	22.0	14.5	37.0	0.021
Vasopressor use on admission (%)	43.5	35.1	60.7	0.025
ICU reason for admission				
Medical (%)	52.0	47.1	62.5	
Surgical (%)	24.0	23.5	23.5	
Trauma (%)	24.0	29.4	12.5	0.164

Table 2. Patients' baseline laboratory data and APACHE score.

n = 103 patients	Total	BNP <300 pg/mL ⁻¹	BNP ≥300 pg/mL ⁻¹	P value
Hemoglobin (g/dL ⁻¹)	11.1±2.0	11.2±2.1	10.8±1.9	0.409
Glycemia (mg/dL ⁻¹)	132.3±56.7	128.8±57.8	140.0±54.5	0.365
eGFR (mL.min ⁻¹ /m ⁻²)	67.8±40.2	80.1±40.4	41.8±24.2	<0.001
Sodium (mmol/L ⁻¹)	141.2±6.6	141.6±6.3	140.4±7.3	0.432
Mean arterial pressure (mm Hg)	62.5±16.8	64.2±16.7	58.5±16.6	0.132
Heart rate (beats per minute)	101.7±23.6	102.1±24.1	100.9±22.7	0.825
Mean BNP (pg/dL ⁻¹)	462±857	99.4±80.5	1269.3±1196.2	<0.001
Median BNP (pg/dL ⁻¹)	43 [159-410]	76 [28-161]	946 [430-1442]	<0.001
Lactate (mg/dL ⁻¹)	1.5 [1.1-2.3]	1.4 [1.1-2.0]	1.9 [1.2-2.3]	0.104*
Troponin I (µg/mL ⁻¹) (N=77)	0.08 [0.03-0.30]	0.04 [0.02-0.16]	0.24 [0.09-1.30]	<0.001*
C-reactive protein (mg/dL ⁻¹)	15.0±12.3	14.9±12.6	15.2±11.8	0.928
CVP (mmHg)	9±6	8±5	11±6	0.020
Vasopressor on admission	43.5 %	35.1%	60.7%	0.025
%APACHE II score	16.2±7.2	15.3±6.1	18.2±8.9	0.013

* Mann-Whitney test; CVP, central venous pressure. All laboratory measurements were taken within one hour of ICU admission. Lactates were collected on the admission arterial blood gas analysis (radial or femoral artery).

Table 3. Echocardiographic data on the first 24 h of admission.

n = 43 patients	Total	BNP <300 pg/mL ⁻¹	BNP ≥300 pg/mL ⁻¹	P value	Spearman r	P value
LVEF (%)	39.8±9.2	42.6±8.2	33.3±8.3	0.001	- 0.405	0.008
TR (mmHg)	43.9±14.5	39.7±13.5	52.9±12.7	0.010	0.284	0.104
LA (mm)	42.5±8.5	40.8±6.0	46.4±12.1	0.083	0.187	0.289
LVEDD (mm)	58.0±8.4	57.6±4.1	58.9±14.5	0.666	0.042	0.818

LVEF, left ventricular ejection fraction; TR, tricuspid regurgitant peak velocity gradient; LA, left atrium; LVEDD, left ventricular end-diastolic diameter.

Discussion

The present study shows that BNP is an independent predictor of long-term survival in an unselected cohort of critically ill patients admitted to an ICU, even after adjustment to APACHE II score. There are several reports regarding the intra-hospital and short-term prognostic impact of this biomarker.¹⁶ However, this study extends

those findings as it is the first to our knowledge to demonstrate that BNP also has a strong long-term prognostic impact. Elevated BNP levels on admission were a frequent finding, with more than 60% of patients having abnormal values according to current recommendations,² a similar proportion to other reports.¹⁷ We also verified a wide range of BNP values, as observed in previous studies with NT-pro-BNP.¹⁸⁻²¹

Causes of elevated BNP in critical illness

Although myocardial injury is one of the major factors responsible for the elevation of BNP, other important mechanisms include renal failure and inflammation.¹⁶ As elevated left ventricular wall tension is thought to be the primary mechanism regulating the secretion of BNP, elevated levels can either be due to decompensated pre-existing cardiac disease or

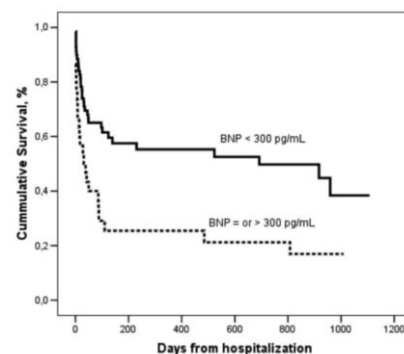


Figure 1. Kaplan-Meier long-term survival plots according to BNP level upon admission.

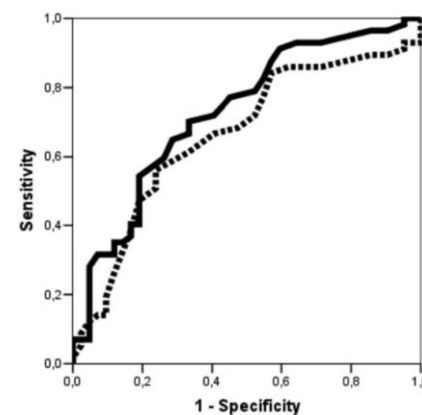


Figure 2. Receiver operating characteristic curve analysis for the entire cohort of critically ill patients. The area under the receiver operating characteristic curve for prediction of long-term survival is 0.727 for the model with BNP and APACHE II score (filled line).

to acute myocardial injury.²² In our cohort, higher BNP was significantly associated with higher prevalence of CAD, HF and hypertension, identifying those patients with a higher risk of mortality. Acute myocardial dysfunction is also an important mechanism for the secretion of natriuretic peptides.²³ In our study, higher BNP levels correlated with higher CVP and troponin I levels, and in the echocardiographic sub-analysis, patients with higher BNP values had also significantly lower LVEF and higher Doppler-derived indices of pulmonary artery pressure. However, these results may reflect a selection bias, as echocardiography was performed only in patients with a clinical indication to do so. Other confounding factors, such as interventions that alter pre- and afterload, like vasopressors (used in 60% of patients), volume resuscitations and mechanical ventilation (in all patients), may all have played a role in the secretion of BNP. In view of the high prevalence of prior heart disease, the association with lower LVEF, higher troponins and higher CVP, the elevated natriuretic peptides levels in the critically ill patients can potentially be of diagnostic and therapeutic importance. Critical illness and sepsis, in particular, are associated with an intense inflammatory response, characterized by markedly increased circulating pro-inflammatory cytokines, associated with elevated levels of BNP in various reports.²⁴ It is known that upregulation of BNP can occur by pro-inflammatory cytokines (as IL-1 beta and TNF-alpha) via p38 MAP kinase.²⁵ The transcription of the BNP gene can also be activated by lipopolysaccharide and its promoter up-regulated by IL-1.²⁶ Interestingly, there was no significant difference in C-reactive protein, as a marker of unspecific inflammatory activation and with prognostic power regarding heart disease²⁷ between groups. Further investigation is warranted to clarify the relation between these two biomarkers. Heart dysfunction and inflammation are not the only factors responsible for elevated BNP levels. Our results demonstrate that eGFR is significantly decreased in patients with BNP 300 pg/mL⁻¹ or over, indicating another important additional mechanism responsible for the elevation of BNP. Previous studies have shown that BNP levels correlate inversely with eGFR in chronic kidney disease and that other factors besides impaired clearance of the peptide, like neuro-hormonal activation and volume status of the patient, can account for BNP elevation.²⁸ Due to its unique profile, BNP can translate a complex crosstalk between the cardiac myocyte, the global volume status and the action of inflammatory cytokines, eventually reflecting the presence of a cardio-renal syndrome (CRS). CRS is defined as a disorder of the heart and kidneys whereby

acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ, as stated in a recent consensus document.²⁹ As biomarkers of integrated cardio-renal burden (a definition recently coined by Yamashita *et al.*) natriuretic peptides may be of use in defining the cardiac part of the CRS³⁰ and help in the diagnosis and prognosis of its various forms, even in patients with various stages of renal insufficiency.³¹ A recent report highlights the usefulness of BNP as a marker for CRS type 4 in ICU patients.³² In the context of the critically non-cardiac patient with simultaneous heart and kidney dysfunction, as in the patient with sepsis (CRS type 5), the measurement of a load-independent biomarker may be useful to assess the cardio-renal burden.

BNP and APACHE II and long-term prognosis

The assessment of prognosis in critically ill patients is a dynamic and very challenging process. Several tools have been developed and the most widely validated is the APACHE II score, a multivariable¹¹ and rather complex system.¹⁷ However, in our analysis, BNP, as a single measurement upon admission, seems to provide complementary long-term prognostic information to that obtained from APACHE II, with a dose-response trend. Our results regarding the discriminatory value of BNP are similar to those reported by Meyer *et al.* in a non-cardiac population regarding short-term survival³³ and extend to long-term prognosis the results of several published observations regarding intra-hospital BNP prognostic value. They can be of particular value in the emergency unit, where rapid decision-making is required for an unselected cohort of critically ill patients.²³ Although the treatment of a post-ACS cohort with normal LVEF but elevated BNP levels with angiotensin-converting enzyme inhibitors (ACEi), direct renin inhibitors or both did not impact on survival in the recently published AVANT GARDE-TIMI 43 trial,²¹ growing evidence indicates that BNP-guided treatment of HF may reduce mortality, especially in younger patients.³⁴ The ability of BNP to integrate several surrogates of poor prognosis, such as advanced age, renal impairment, inflammation and pre-existing LV systolic or diastolic dysfunction, converts it into a weighted sum of different risk markers, meaning its short and long-term prognostic power is derived from this lack of specificity.⁵ The present study, extending the impact of an elevated admission BNP on long-term prognosis, highlights the importance of early detection and careful monitoring of patients with elevation of this biomarker, both during hospitalization and particularly after discharge. Patients with

higher BNP levels on admission may be candidates for an early echocardiogram to detect subclinical heart disease, since clinical signs of HF may be difficult to identify in ICU patients. An early echocardiogram may also indicate cardio-renal disease, prompting the initiation of long-term protective therapies after ICU discharge, such as ACEi or beta-blockers, as many of the patients die in the first 100 to 150 days after discharge.

Study limitations

The relatively small sample size in our study may have limited the associations between the different variables and due to technical limitations, it was not possible to collect echocardiographic data in all patients. We only analyzed admission BNP, but it is known that there are significant changes in BNP and renal function in the first days after admission.¹³ However, this has not compromised its important prognostic power. Although some of the patients had cardiovascular comorbidities that may have had a significant impact on BNP levels (patients with pre-existing CAD, history of congestive HF and chronic supra-ventricular arrhythmias, such as atrial fibrillation), our study population reflects a non-selected cohort that may be found in a polyvalent ICU, highlighting the important role of BNP in signaling the cardio-renal interactions in those patients. Moreover, we used similar inclusion and exclusion criteria to those found in other studies.^{17,33}

Invasive hemodynamic variables other than CVP were not collected, as recent evidence does not support the routine placement of indwelling pulmonary catheters;³⁵ moreover, previous studies had not found a good correlation between natriuretic peptides and left ventricular filling pressures in ICU patients.²³ The impact of cardio-renal protective therapies, instituted after discharge, has not been taken into account. Areas under curve (AUC) for isolated APACHE II score and BNP regarding long-term prognosis were rather low in our population (<0.7). Nevertheless, APACHE II score will continue to be used clinically in this population and as a consequence of these low AUC, the use of a single variable might be insufficient. With the addition of BNP to APACHE II score, the AUC yields a value of 0.73 that is acceptable for clinical decision-making.

Conclusions

The present study demonstrates that in an unselected cohort of ICU patients, admission BNP levels are frequently elevated, even without clinically apparent acute heart disease.

BNP levels correlated well with the severity of disease and had long-term independent prognostic impact on mortality, with an additive effect to the APACHE II risk score. More studies are warranted in larger cohorts to determine if this simple, widely available and non-invasive test is useful to identify patients who can benefit from strategies aimed to suppress the cardio-renal burden on long-term prognosis.

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