

# Predictors of mortality in cardiac surgery: brain natriuretic peptide type B

*Preditores de mortalidade em cirurgia cardíaca: peptídeo natriurético cerebral tipo B*

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## Abstract

**Objective:** We evaluated whether the preoperative serum concentration of brain natriuretic peptide (BNP) is a predictor of in-hospital mortality in patients that underwent cardiac surgery.

**Methods:** We continuously evaluated 488 patients that underwent cardiac valve surgery or coronary artery bypass grafting (CABG) between January of 2009 and July of 2012. Follow up of these patients were done prospectively for 30 days postoperatively.

**Results:** Data analysis showed that the overall mortality rate was equal to 9.6%, Receiver Operating Characteristic (ROC) curve analysis found the optimal cut-off value of BNP equal to 382 pg/mL for overall mortality (AUC=0.73, 95% CI=0.66 to 0.81,  $P<0.001$ ). Multivariate analysis showed that the value of BNP higher than 382 pg/mL ( $P=0.033$ , HR=2.05, 95% CI=1.6 to 3.98) was an independent predictor of overall mortality at 30 days postoperatively.

**Conclusion:** We concluded that the preoperative serum concentration of BNP is an independent predictor of mortality in patients undergoing valve surgery or coronary artery bypass graft.

**Descriptors:** Natriuretic Peptides. Hospital Mortality. Cardiovascular Surgery Procedures. Prospective Studies.

## Resumo

**Objetivo:** Avaliar se a concentração sérica pré-operatória de peptídeo natriurético cerebral tipo B (BNP) é preditora de mortalidade intra-hospitalar em pacientes submetidos à cirurgia cardíaca.

**Métodos:** Foram avaliados 488 pacientes consecutivamente submetidos à cirurgia cardíaca valvar ou à cirurgia de revascularização do miocárdio no período de janeiro de 2009 a julho de 2012. Estes foram seguidos, prospectivamente, por 30 dias de pós-operatório.

**Resultados:** Em nossa casuística, a mortalidade geral foi igual a 9,6% e 52% dos pacientes foram submetidos a cirurgia de revascularização do miocárdio. Análise de curva ROC (Receiver Operating Characteristic) encontrou o valor de corte ótimo de BNP igual a 382 pg/mL para mortalidade geral (AUC=0,73, IC95%=0,66 a 0,81,  $P<0.001$ ). Análise multivariada mostrou que o valor de BNP > 382 pg/mL ( $P=0,033$ , HR=2,05, IC 95%=1,06 a 3,98) foi preditor independente de mortalidade geral em 30 dias de pós-operatório.

**Conclusão:** A concentração sérica pré-operatória do BNP é um preditor independente de mortalidade em pacientes submetidos à cirurgia valvar ou de revascularização do miocárdio.

**Descritores:** Peptídeos Natriuréticos. Mortalidade Hospitalar. Procedimentos Cirúrgicos Cardiovasculares. Estudos Prospectivos.

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| Abbreviations, acronyms & symbols |                                   |
|-----------------------------------|-----------------------------------|
| AUC                               | Area under ROC curve              |
| BNP                               | Brain natriuretic peptide         |
| CABG                              | Coronary artery bypass grafting   |
| CI                                | Confidence interval               |
| HR                                | Hazard ratio                      |
| LV                                | Left ventricle                    |
| ROC                               | Receiver Operating Characteristic |

## INTRODUCTION

In the last decade, the interest in the use of brain natriuretic peptide (BNP) levels as a risk stratification tool in patients undergoing cardiac surgery has increased<sup>[1-3]</sup>. In the clinical setting, risk scoring systems are widely validated and used as the gold standard method of evaluation of risk of perioperative mortality. On the other hand, these systems were proved to be complex with limited accuracy for certain cohorts of patients<sup>[4,5]</sup>. Consequently, new markers able to stratify risk and predict higher mortality rate in cardiac surgery are being investigated.

In addition to be used as a parameter to assess and validate the prognosis in several clinical situations, the measurement of BNP serum concentration has low cost, is easily performed and highly available, and has good reproducibility<sup>[6-8]</sup>. Up to this the moment, few studies have evaluated the serum concentration of preoperative BNP as a predictor of mortality in cardiac surgery, mainly due to the heterogeneity of small sample size, making it impossible to consistently assess its relation to mortality<sup>[1-3]</sup>. Thus, additional studies have become necessary to demonstrate the correlations between BNP levels and mortality in cardiac surgery. In this study, the aim was to assess whether the preoperative BNP can be used as an independent predictor of mortality in cardiac surgery.

## METHODS

The study evaluated 488 patients admitted to the Postoperative Cardiac Intensive Care Unit in the Medical School of Sao Jose do Rio Preto/Hospital of Base for heart valve surgery or coronary artery bypass grafting between January of 2009 and June of 2012. Exclusion criteria included patients younger than 18 years old, with advanced malignancy or who had undergone combined cardiac procedures. Data were collected prospectively by consulting the computerized database Hospital de Base of São José do Rio Preto - SP - Brazil. This hospital is a reference center for the treatment of cardiovascular diseases and serves a region of about 1.5 million people. The study was approved by the Ethics Committee of the Medical School of São José do Rio Preto (Protocol Number 6079/2010) and due to the nature of the study, no informed consent was required.

The data included demographic, comorbidities, degree of left ventricular systolic dysfunction, intraoperative variables and mor-

tality from all causes within 30 days postoperatively. All variables were defined according to the latest guidelines published by the American Heart Association and European Society of Cardiology.

The serum concentration of BNP was measured in the preoperative period immediately before all operations, by the method of electrochemiluminescence using the Siemens AD-VIA Centaur equipment (Siemens Medical).

Categorical variables were presented as absolute numbers (percentages) and continuous variables as median and interquartile range.

Statistical analysis was performed with SPSS software (version 20.0). The discriminating power of the value of preoperative serum concentration of BNP to predict mortality from all causes in 30 days after surgery was determined with the aid of statistical C by calculating the area under the ROC curve ("Receiver Operating Characteristic"), with the value > 0.60 considered not determined by chance.

In this study, proportional regression risk analysis of Cox was used to establish the relationship between the dependent variable (mortality from all causes) and the exploratory variables. Single variables associated with mortality (*P* value ≤0.05) were considered for multivariate regression analysis. The Spearman test was used to correlate continuous variables when two or more variables were closely correlated, the one with the highest statistical value of Wald was selected for multivariate analysis. Independent predictors of mortality were established for variables with *P* ≤ 0.05 in multivariate analysis.

The stepwise logistic regression method with likelihood ratio was used to determine independent predictors of mortality from all causes in the multivariate analysis. The probability of survival, as well as risk functions were estimated by the Kaplan-Meier method. The log rank test was used to compare the probability of survival between groups.

Values with *P* ≤ 0.05 were considered statistically significant.

## RESULTS

### Baseline characteristics of patients

From January of 2009 to June of 2012, 488 consecutive patients undergoing coronary artery bypass grafting or isolated valve surgery were included in the study.

The baseline characteristics evaluated in this study are summarized in Table 1. The median age was 57 (49-65) years and 58% were men. From the 488 patients, 92 (19%) were diabetic, 328 (67%) had systemic arterial hypertension. One hundred twenty-six patients (26%) had emergency surgery, 70 patients (14%) had at least one previous cardiac surgery and 80 patients (16%) had left moderate or severe ventricular dysfunction, the preoperative serum creatinine concentration and the preoperative clearance of creatinine were 1.1 mg/dl (0.9 to 1.3) and 68.5 mL/min/1.73 m<sup>2</sup> (52.6 to 87.4), respectively. Isolated valve surgery was performed in 236 patients (48%) and coronary artery bypass surgery in 252 patients (52%), with 457 operations

Table 1. Baseline characteristics of patients included in the study (n = 488).

| Variables  | Values           |
|--|------------------|
| Age, years, median (Q1-Q3)                                     | 57 (49-65)       |
| Male, n (%)  | 284 (58)         |
| Systemic Arterial Hypertension, n (%)                          | 328 (67)         |
| Chronic Obstructive Pulmonary Disease                          | 16 (3.3)         |
| Diabetes Mellitus, n (%)                                       | 92 (19)          |
| Urgent or emergency surgery, n (%)                             | 126 (26)         |
| Body mass index, median (Q1-Q3)                                | 26 (23-29)       |
| Moderate or severe LV dysfunction, n (%)                       | 80 (16)          |
| Previous Surgery, n (%)  | 70 (14)          |
| Preoperative serum creatinine (mg/dl)                          | 1.1 (0.9-1.3)    |
| Preoperative creatinine clearance (ml/min/1.73m <sup>2</sup> ) | 68.5 (52.6-87.4) |
| Preoperative BNP, pg/ml, median (Q1-Q3)                        | 239 (80-786)     |
| Additive EuroSCORE, median (Q1-Q3)                             | 3 (2-5)          |
| Coronary Artery Bypass Surgery, n (%)                          | 252 (52)         |
| Valve surgery, n (%)   | 236 (48)         |
| Preoperative troponin I, median (Q1-Q3)                        | 0.1 (0.01-1.1)   |
| Use of intra-aortic balloon, n (%)                             | 31 (6.4)         |
| Number of coronary grafts, median (Q1-Q3)                      | 3 (2-3)          |
| Use of extracorporeal circulation, n (%)                       | 457 (94)         |
| Extracorporeal circulation time, min, median (Q1-Q3)           | 98 (81-120)      |

LV=Left ventricle; BNP=brain natriuretic peptide

(94%) performed with cardiopulmonary bypass, with the median of cardiopulmonary bypass time equal to 98 (81-120) minutes. The median value of additive EuroSCORE was 3 (2-5).

**Mortality from all causes at 30 days postoperatively**

The area under the ROC curve was 0.74 (95% CI 0.66 to 0.81) for preoperative serum BNP with a cut-off value of 382 pg/mL, with a sensitivity of 72% and specificity equal to 64% for predicting death from all causes in 30 days after surgery (Figure 1).

In univariate analysis, age ( $P<0.001$ ), urgency or emergency surgery ( $P<0.001$ ), left moderate or severe ventricular dysfunction ( $P=0.026$ ), previous surgery ( $P<0.001$ ), preoperative serum BNP>382 pg/mL ( $P<0.001$ ), clearance of preoperative creatinine ( $P<0.001$ ) and cardiopulmonary bypass time ( $P<0.001$ ) were retained to multivariate analysis. The age ( $P<0.001$ , HR = 1.05; 95% CI 1.02 to 1.09), urgent or emergency surgery ( $P=0.027$ , HR=1.98, 95% CI 1.08 to 3.64), preoperative serum BNP> 382 pg/mL ( $P=0.033$ , HR=2.05, 95% CI 1.06 to 3.98), clearance of preoperative creatinine ( $P<0.001$ , HR=0.97; 95% CI 0.96 to 0.99) and cardiopulmonary bypass time ( $P<0.001$ , HR=1.02, 95% CI 1.01 to 1.02) variables were retained as predictors independent of death from all causes after multivariate Cox regression analysis (Table 2).

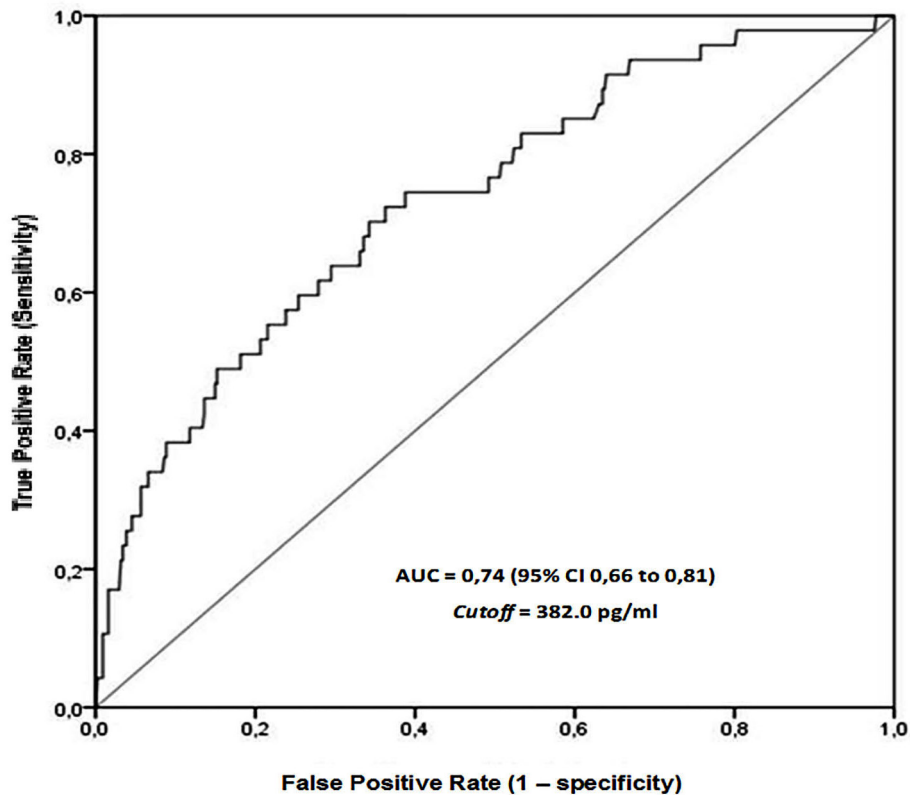


Fig. 1 - ROC (Receiver Operating Characteristic) curve relating preoperative serum brain natriuretic peptide (BNP) and mortality from all causes.

Table 2. Uni and multivariate analysis of the variables in relation to mortality.

| Variabes                                 | P value | Hazard Ratio | 95%CI       |
|--|---------|--------------|-------------|
| Univariate model                         |         |              |             |
| Age                                      | <0.001  | 1.074        | 1.043-1.105 |
| Male                                     | 0.317   | 0.075        | 0.421-1.323 |
| Systemic Arterial Hypertension           | 0.286   | 1.429        | 0.742-2.752 |
| Chronic Obstructive Pulmonary Disease    | 0.213   | 2.104        | 0.653-6.776 |
| Diabetes Mellitus                        | 0.406   | 1.332        | 0.678-2.616 |
| Urgent br emergency surgery              | <0.001  | 3.882        | 2.184-6.900 |
| Body mass index                          | 0.908   | 1.003        | 0.948-1.062 |
| Moderate or severe LV dysfunction        | 0.026   | 2.067        | 1.091-3.917 |
| Previous Surgery                         | <0.001  | 3.025        | 1.638-5.586 |
| BNP preoperative > 382 pg/ml             | <0.001  | 3.89         | 2.082-7.270 |
| Preoperative creatinine clearance        | <0.001  | 0.96         | 0.94-0.97   |
| Extracorporeal circulation time, minutes | <0.001  | 1.017        | 1.012-1.021 |
| Multivariate model                       |         |              |             |
| Age                                      | <0.001  | 1.081        | 1.050-1.114 |
| Urgent or emergency surgery              | 0.02    | 2.039        | 1.116-3.726 |
| Extracorporeal circulation time, minutes | <0.001  | 1.017        | 1.012-1.023 |
| Preoperative creatinine clearance        | <0.001  | 0.97         | 0.96-0.99   |
| BNP preoperative > 382 pg/ml             | 0.034   | 2.059        | 1.056-4.015 |

LV=Left ventricle; BNP=brain natriuretic peptide; CI=confidence interval

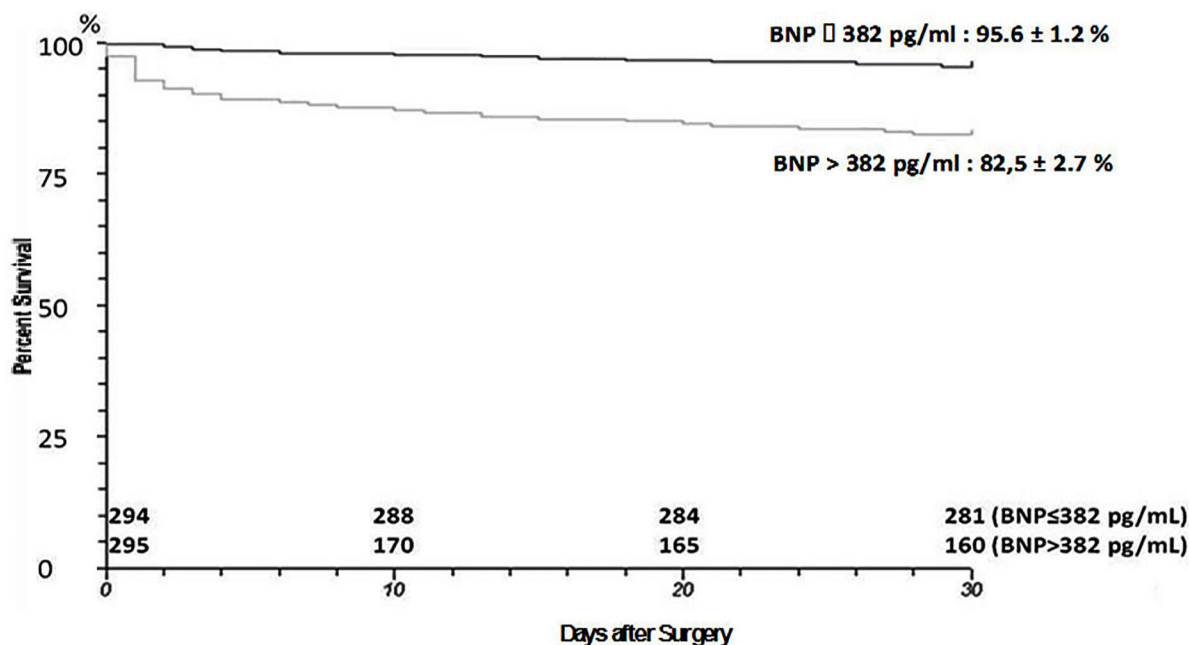


Fig. 2 - Kaplan-Meier's curve for survival at 30 days postoperatively. BNP=brain natriuretic peptide

Figure 2 illustrates the 30-day survival probability of patients who were divided into groups according to the BNP values being lower than or equal to 382 pg/ml or greater than 382 pg/ml, respectively, with the values being 95.6% and 82.5% at 30 days after surgery ( $P < 0.001$ ).

## DISCUSSION

In this prospective and contemporary study of patients undergoing cardiac surgery the preoperative serum concentration of BNP was correlated to postoperative mortality. Al-

though there are several known risk factors of mortality in cardiac surgery, the association between preoperative BNP and mortality in cardiac surgery is still under investigation<sup>[1]</sup>. We found that preoperative BNP is an independent predictor of postoperative mortality in cardiac surgery. This assertion is based on the *P* value obtained by Cox regression analysis, in addition to the significant difference in the probability of survival between the groups stratified according to BNP. This finding demonstrates a role for BNP regarding the evaluation of preoperative risk in cardiac surgery.

Few studies have described the prognostic significance of preoperative BNP in the heart surgery setting<sup>[1-3]</sup>. In a meta-analysis recently published the preoperative BNP was evaluated as a predictor of adverse outcomes in cardiac surgery, among 819 relevant studies identified in the literature, only four associated preoperative serum BNP with mortality and of these, only one has examined this relationship with the help of multivariate analysis<sup>[1]</sup>. In this small study mentioned (n=209), BNP was an independent predictor of adverse cardiac events, described as combined event of death and non-fatal events (malignant ventricular arrhythmia, myocardial infarction and heart failure)<sup>[9]</sup>. In the present study, we found that preoperative BNP was an independent predictor of mortality from all causes with methodology specifically geared to this goal to become a pioneering study in relation to its results.

Our group believes that the prognostic value of preoperative BNP is due to its ability to measure ventricular hemodynamic changes even in asymptomatic patients<sup>[10]</sup>. Discovered in 1988, only in 1994 a study was performed to assess the site and mechanism of secretion of BNP, showing that higher BNP levels were significantly correlated with increased pulmonary capillary wedge pressure, increased diastolic and end systolic ventricular volume of the left ventricle, lower left ventricular ejection fraction and a lower cardiac index<sup>[11-14]</sup>. Consequently, it was concluded that secretion is stimulated by increased ventricular wall stress and correlates with increased cardiovascular risk variables<sup>[10,11,15]</sup>. Our group believes that this pathophysiological mechanism intrinsically related to secretion of BNP is the explanation for the higher levels of preoperative BNP are independently associated with increased mortality in cardiac surgery.

Score systems are widely used in preoperative risk stratification with emphasis on choosing the best method of treatment according to the risk found, and performed an uniform comparative analysis between different surgeons and centers specialized in heart surgery<sup>[16,17]</sup>. However, conducts aiming to reduce perioperative risk are rarely adopted based on these risk scores because they are made up of a large number of variables, and do not have a progressive nature to assess pre-surgical procedures<sup>[18]</sup>. Therapies guided by BNP levels have been effective in reducing hospitalization and death in patients with heart failure<sup>[19]</sup>. Therefore, BNP can provide a noninvasive indicator to evaluate the effectiveness of

perioperative hemodynamic reductions in stress related to blood volume status of these patients aiming at better risk stratification and optimization of surgical outcomes.

This study was designed to assess the association between the value of preoperative serum BNP and mortality in patients undergoing valve replacement surgery or coronary artery bypass graft surgery. Compared to the other existing studies in this area, this study has the highest number of participants with clinically relevant result to demonstrate that preoperative BNP was an independent predictor of the outcome of isolated postoperative mortality in cardiac surgery. However, our study has limitations, such as the fact that it was performed at a single medical center with short-term follow-up.

Further studies are needed to assess the association between preoperative serum BNP and mortality in cardiac surgery, because the data are limited regarding this issue. Our study adds information to the limited literature and suggests that the BNP preoperative serum concentration should be included in all future studies that assess mortality in cardiac surgery as a clinical outcome.

## CONCLUSION

It was demonstrated that the high levels of preoperative BNP were an independent predictor of 30-day mortality after surgery for patients undergoing heart valve surgery or coronary artery bypass graft. This finding raises the possibility that targeted therapy for the reduction of BNP can be effective in reducing mortality in cardiac surgery.

| Authors' roles & responsibilities |  |
|-----------------------------------|--|
| JAMJ                              | Analysis and/or interpretation of data; statistical analysis; final approval of the manuscript; study design; operations and/or experiments conduct; writing of the manuscript or critical review of its content |
| MAN                               | Analysis and/or interpretation of data; study design   |
| MNM                               | Analysis and/or interpretation of data; statistical analysis; final approval of the manuscript; study design; writing of the manuscript or critical review of its content  |
| MFG                               | Analysis and/or interpretation of data; statistical analysis; final approval of the manuscript; study design; writing of the manuscript or critical review of its content  |

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