

Association between the level of plasma B-type natriuretic peptide and in-hospital mortality in patients with acute exacerbation of COPD without a history of coronary ischemic heart disease: a retrospective study

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Abstract

Background: Previous studies suggested that plasma B-type natriuretic peptide (BNP) level was often elevated in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and was associated with increased mortality. However, most studies did not consider the fact that conditions such as coronary ischemic heart disease can also increase BNP level. Therefore, we aimed to explore the association between BNP level and in-hospital mortality in patients with AECOPD without a history of coronary ischemic heart disease.

Methods: In this retrospective cohort study, patients who were diagnosed with AECOPD using International Statistical Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9 codes) between January 2017 and December 2019. All data were obtained from electronic patient files and medical data intelligence platform of Jinan Central Hospital. BNP level was determined within 24 hours after admission, and the value was \log_2 transformed. The primary outcome was in-hospital mortality, and the secondary outcome was a composite outcome of in-hospital mortality or invasive mechanical ventilation.

Results: A total of 300 patients were included in this study. Univariate cox regression analysis showed that the unadjusted HRs of the primary and secondary outcomes were 1.85 (95% CI, 1.39-2.47) and 1.45 (95% CI, 1.20-1.75), respectively. After adjustment for age, sex, past medical history, smoking status, drinking status, CURB65 (Confusion, Urea > 7mmol/L, Respiratory rate \geq 30/min, Blood pressure systolic < 90 mmHg or diastolic < 60 mmHg and age > 65 years), arterial partial pressure of O_2 (PaO₂), the adjusted HRs of the primary and secondary outcomes were 3.65 (95% CI, 2.54-5.26) and 1.43 (95% CI, 1.14-1.97), respectively. The results of subgroup analysis by age, sex, and lung function were robust. This study was retrospective, so there was no clinical trial registration.

Conclusions: The plasma \log_2 BNP level was significantly associated with in-hospital mortality and a composite outcome of in-hospital mortality or invasive mechanical ventilation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a global public health challenge because of its high prevalence and the related disability and mortality.^[1] COPD has become the third leading cause of death worldwide and is estimated to become the source of the seventh highest burden worldwide in 2030.^[2] Prevalence was higher in men than in women, and in individuals aged \geq 40 years, it was 13.7% in China;^[1] 6.4% of Americans reported receiving a diagnosis of COPD.^[3]

Plasma brain natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide (BNP; NT-pro-BNP) are cardiac neurohormones that are synthesized and released from ventricular myocytes in response to myocardial stretching.^[4] It had been proven that BNP and NT-pro-BNP are diagnostic and prognostic biomarkers of congestive heart failure^[5] and established that BNP and NT-pro-BNP are independent predictors of death and cardiovascular events in patients with stable coronary artery disease.^[6]

Furthermore, they were found to be elevated with right ventricular overload and to be associated with a poor prognosis in patients with pulmonary arterial hypertension and pulmonary thromboembolism.^[7-9]

Previous studies have shown that BNP and NT-pro-BNP are probably useful in predicting the outcomes of COPD. A prospective, single-center study on acute exacerbation of COPD (AECOPD) suggested that elevated NT-pro-BNP level was associated with an increase in 30-day mortality.^[10] Another prospective study showed that NT-pro-BNP level was associated with in-hospital mortality and 1-year mortality in patients with exacerbations of COPD; however, in their studies, about 35.9% of patients had congestive heart failure.^[11] Stolz et al. found that BNP accurately predicted the need for intensive care unit (ICU) treatment,^[12] and BNP was an independent predictor of requirement for noninvasive ventilation, mechanical ventilation, and noninvasive ventilation failure in patients with AECOPD along with preserved left ventricular function.^[13] However, some studies have found that NT-pro-BNP level was not associated with the requirement for noninvasive positive pressure ventilation, mechanical ventilation, or in-hospital mortality in patients with AECOPD without underlying left ventricular dysfunction.^[14]

We aimed to assess the association between BNP level and in-hospital mortality or requirement for invasive mechanical ventilation in patients hospitalized for AECOPD without a history of coronary ischemic heart disease.

Methods

Ethics Committees of Jinan Central Hospital reviewed and approved this retrospective study protocol in accordance with the precepts established by the Declaration of Helsinki (the assurance number 2020-137-01), and waived the need for obtaining informed consent from patients.

Data Sources

All data were obtained from electronic patient files and medical data intelligence platform of Jinan Central Hospital. The medical data intelligence platform is administered by Jinan Central Hospital, which is a comprehensive hospital with 2000 beds and a teaching hospital affiliated to medical university, and all local in-patient and out-patient information was registered in it since January 2009.

Study Patients and Covariates

In this retrospective cohort study, patients who were diagnosed with AECOPD using International Statistical Classification of Diseases and Related Health Problems, Ninth Revision (ICD-9 codes) between January 2017 and December 2019 were included (explicit ICD-9 codes J44.0, J44.1 and J44.9). Patients were included if they met the eligibility criteria: (1) ages ≥ 40 years; (2) primary discharge diagnosis of AECOPD; (3) spirometry supported diagnosis of COPD (FEV1/FVC $< 70\%$). Lung function measured at disease stability (defined as either within 6 months prior to the exacerbation or 6 weeks after recovery). Exclusion criteria included: (1) a discharge diagnosis including acute asthma, bronchiectasis, bronchogenic carcinoma, and acute myocardial infarction; (2) with a medical history of coronary ischemic heart disease

and advanced renal disease. If patients were admitted more than once during the study period, only the first admission was included in the analysis.

We obtained demographic data (including age, gender, smoking status, drinking status, past medical history and lung function), physiological variables (including consciousness, pulse, respiratory rate, blood pressure systolic and blood pressure diastolic) and laboratory parameters (including arterial blood gas, serum urea and creatinine, serum albumin, D-dimer, CRP and BNP) that were recorded on admission. If laboratory parameters were measured more than once during the in-hospital stay, data obtained from the first measurement within 24 h of admission alone were collected. Routine blood test results on admission before antibiotic treatment. In this retrospective cohort study, there were 2 outcomes of interest, primary outcome, in-hospital mortality; secondary outcomes, (1) a composite outcome of in-hospital mortality or invasive mechanical ventilation and (2) invasive mechanical ventilation.

Statistical Analysis

Continuous variables with normal distribution are presented as mean \pm standard deviation (SD). Non-normally distributed variables are presented as median (interquartile range [IQR]). Categorical variables are presented as percentage. Differences between groups were compared using the Kruskal-Wallis test for continuous variables or Wilcoxon-Mann-Whitney Test for categorical variables. BNP was \log_2 transformed. Outcomes were compared using cox regression, both unadjusted and adjusted. Adjusted models included the following covariates: age; sex; smoking status of never, ex-smoker, and current smoking; drinking status of never, ex-drinker, and current drinker; past medical history of hypertension, diabetes, cerebral vascular disease, renal dysfunction, atrial fibrillation, and malignancy; variables with $p \leq 0.1$ in univariate analysis (CURB65, arterial partial pressure of O_2 [PaO_2]). Subgroup analyses (by sex, age and missing of lung function) were performed, and differences in HRs between subgroups were tested by Wald tests for statistical interaction. Statistical analysis was performed using Packages R (The R Foundation, Vienna, Austria); a statistical significance level of 0.05 was used.

Results

In this retrospective cohort study designed to examine the association of BNP level with the outcomes of patients with AECOPD, medical records of 722 patients hospitalized with AECOPD were reviewed, and those on 300 patients were included. Patient selection is shown in the Figure 1. The demographic and baseline characteristics of all the included patients are shown in Table 1. Among the patients, 63.33% were men. The mean age of patients was 76.88 ± 9.53 years. Sixteen patients died during hospitalization and 28(9.33%) patients were assisted with invasive mechanical ventilator. The duration of hospital stay was 12.04 ± 6.35 days. BNP levels of 300 (100%) patients were available. Its median was 65.50 pg/ml (IQR, 30.00, 181.50), Figure 2 showed the distribution of BNP in different patients.

In univariate cox regression analysis, we used all baseline variables of the entire cohort to assess factors associated with the primary outcome (Table 2) and the secondary outcomes (supplementary files Table 2b and Table 2c). Table 3 shows the unadjusted and adjusted HRs from the Cox regression analysis. A higher

\log_2 BNP value was significantly associated with a greater risk of in-hospital mortality in the unadjusted analysis (HR, 1.85 [95% CI, 1.39-2.47]), and the association was still significant after accounting for age, sex, smoking status, drinking status, past medical history, CURB65, and PaO₂ (HR, 3.65 [95% CI, 2.54-5.26]).

The secondary outcome of in-hospital mortality or invasive mechanical ventilation was observed 10.33% (31/300). Table 3 shows the unadjusted and adjusted HRs derived from the Cox regression analysis. As in the case of the primary outcome of in-hospital mortality, a higher \log_2 BNP value was significantly associated with a higher risk of the combined end point of in-hospital mortality or invasive mechanical ventilation in unadjusted analysis (HR, 1.45 [95% CI, 1.20-1.75]), and this association was still significant after adjusting for age, sex, smoking status, drinking status, past medical history, CURB65, and PaO₂ (HR, 1.43 [95% CI, 1.11-1.84]).

Table1: Cohort characteristics of the study patients

Variables	All (n=300)
Sex, n (%)	
male	190 (63.33)
female	110 (36.67)
Age, mean in years (SD)	76.88 (9.53)
Smoking status, n (%)	
Never	104 (34.67)
Ex-smoker	156 (52.00)
Current smoking	40 (13.33)
Drinking status, n (%)	
Never	193 (654.33)
Ex-drinker	90 (30.00)
Current drinker	17 (5.67)
Past medical history	
Hypertension, n (%)	79 (26.33)
Diabetes, n (%)	35 (11.67)
Cerebral vascular disease, n (%)	38 (12.67)
Renal dysfunction, n (%)	4 (1.33)
Malignancy, n (%)	7 (2.33)
Atrial fibrillation, n (%)	10 (3.33)
Duration of hospital stay, mean in days (SD)	12.04 (6.35)
Lung function, mean (SD)	
FVC (litres)	2.95 (0.71)
FEV1 (litres)	2.22 (0.63)
FEV1 (%predicted)	70.39 (19.75)
FEV1/FVC (%)	56.38 (10.41)
Clinical scores	
CURB65, mean (SD)	1.24 (0.69)
BAP, mean (SD)	2.33 (0.73)
BMI	24.15 (4.14)

Arterial blood gas	
PaCO ₂	49.47 (17.67)
PaO ₂	79.74 (26.08)
pH	7.39 (0.08)
Neutrophil count, ×10 ⁹ /l	6.70 (4.25)
CRP, mg/l	13.55 (3.48, 41.40)
Creatinine, umol/l	68.50 (56.60, 87.10)
Urea, mmol/l	5.20 (4.00, 6.70)
Albumin, g/l	37.90 (4.96)
D-dimer, mg/l	0.54 (0.31, 1.33)
BNP, pg/ml	65.50 (30.00, 181.50)
Invasive ventilation	28 (9.33)
In-hospital mortality	16 (5.33)
In-hospital mortality or invasive ventilation	31 (10.33)

Abbreviations: CRP, C reactive protein; BMI, body mass index; PaO₂, arterial partial pressure of O₂; PaCO₂, arterial partial pressure of CO₂; BNP, plasma B-type natriuretic peptide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

The secondary outcome of invasive mechanical ventilation was observed in 9.33% (28/300) of patients. Table 3 shows the unadjusted and adjusted HRs derived from the Cox regression analysis. As in the case of the primary outcome of in-hospital mortality, a higher log₂BNP value was significantly associated with a higher risk of invasive mechanical ventilation in unadjusted analysis (HR, 1.51 [95% CI, 1.24-1.85]), and this association was still significant after adjusting for age, sex, smoking status, drinking status, past medical history, CURB65, and PaO₂ (HR, 1.50 [95% CI, 1.14-1.97]).

In this study, among patients with AECOPD, subgrouping was performed according to (1) sex, (2) age, and (3) missing lung function data were examined. The results were similar to the overall results, and all tests for interaction with these covariates were not statistically significant (P >0.05) (Table 4).

In the study, C-reactive protein level, findings of arterial blood gas test, and lung function data were partially missing, but the missing data was processed. Sensitivity analysis of deleting the missing data of arterial blood gas showed that there was no significant difference in the findings of univariate and multivariable cox regression models (Table 2s and Table 3s).

Discussion

Among patients diagnosed with exacerbations of COPD, this study found significant association between \log_2 BNP and in-hospital mortality, a composite outcome of in-hospital mortality or mechanical ventilation, and mechanical ventilation, after adjusting for baseline demographics, comorbidities and other hematological data; results of the subgroup analysis were stable; and this suggests that BNP can be used as an important biomarker of prognosis in patients with COPD exacerbations.

Table 2: Univariate associations with in-hospital mortality

Variables	All (n=300)	P Value
Sex, n (%)		
female	110 (36.67)	1.0
male	190 (63.33)	0.573
Age, mean in years (SD)	76.88 (9.53)	0.191
Smoking status, n (%)		
Never	104 (34.67)	1.0
Ex-smoker	156 (52.00)	0.301
Current smoking	40 (13.33)	0.050
drinking status, n (%)		
Never	193 (64.33)	1.0
Ex-drinker	90 (30.00)	0.362
Current drinker	17 (5.67)	0.374
Past medical history		
Hypertension, n (%)	79 (26.33)	0.701
Diabetes, n (%)	35 (11.67)	0.311
Cerebral vascular disease, n (%)	38 (12.67)	0.154
Renal dysfunction, n (%)	4 (1.33)	NA
Malignancy, n (%)	7 (2.33)	0.430
Atrial fibrillation, n (%)	10 (3.33)	0.062
Lung function, mean (SD)		
FVC (litres)	2.95 (0.71)	0.659
FEV1(litres)	2.22 (0.63)	0.551
FEV1(%predicted)	70.39 (19.75)	0.204
FEV1/FVC (%)	56.38 (10.41)	0.421
Clinical scores		
CURB65, increment by 1	1.24 (0.69)	0.017
BAP, increment by 1	2.33 (0.73)	0.121
BMI	24.15 (4.14)	0.480
PaCO ₂	49.47 (17.67)	0.993

PaO₂	79.74 (26.08)	0.017
pH	7.39 (0.08)	0.532
Neutrophil count, ×10 ⁹ /l	6.70 (4.25)	0.189
CRP, mg/l	37.56(67.09)	0.535
Creatinine, umol/l	78.26 (43.24)	0.732
Urea, mmol/l	6.07 (3.96)	0.166
Albumin, g/l	37.90 (4.96)	0.125
D-dimer, mg/l	1.17 (1.67)	0.412
BNP, pg/ml	207.82 (378.35)	0.002

Abbreviations: CRP, C reactive protein; BMI, body mass index; PaO₂, arterial partial pressure of O₂; PaCO₂, arterial partial pressure of CO₂; BNP, plasma B-type natriuretic peptide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

A previous prospective study by Chang et al. found that elevated NT-pro-BNP levels (>220 pmol/L) were associated with increased 30-day mortality, and this finding is consistent with that of our study.^[10] Another study by Hai et al. found that NT-pro-BNP level (≥551.35 ng/l) was associated with in-hospital mortality and 1-year mortality in patients with exacerbations of COPD, but in their study, about 35.9% of patients had congestive heart failure.^[11] A systematic review and meta-analysis also found that elevated NT-pro-BNP values were associated with all-cause in-hospital mortality in patients with and without exacerbation of COPD.^[17]

Table 3. Hazard ratios for log₂BNP and in-hospital mortality, composite of in-hospital mortality or invasive ventilation, invasive ventilation

	No. (%)	Unadjusted model	Age-and sex-adjusted model	Fully adjusted model*
		HR (95% CI) <i>P</i> -value	HR (95% CI) <i>P</i> -value	HR (95% CI) <i>P</i> -value
Primary outcome				
In-hospital mortality	16(5.33)	1.85 (1.39, 2.47) <0.001	2.00 (1.44, 2.77) <0.001	3.65 (2.54, 5.26) <0.001
Secondary outcomes				
Mortality or invasive ventilation	31 (10.33)	1.45 (1.20, 1.75) <0.001	1.50 (1.23, 1.82) <0.001	1.43 (1.11, 1.84) 0.006
Invasive ventilation	28 (9.33)	1.51 (1.24, 1.85) <0.001	1.57 (1.27, 1.93) <0.001	1.50 (1.14, 1.97) 0.004

*fully adjusted model includes the following covariates: age, sex, smoking status, drinking status, past medical history, CURB65, PaO₂.

Stolz et al. found that BNP was not associated with 6-month or 2-year mortality in patients with exacerbations of COPD, but BNP accurately predicted the need for ICU treatment, and the need for mechanical ventilation was the most common reasons for ICU admission.^[12] This is confirmed in our study, we also found that the association between log₂BNP and invasive mechanical ventilation was strong in multivariate analysis. This was consistent with the finding of previous studies in which BNP was an independent predictor of higher noninvasive ventilation requirement, mechanical ventilation use, and noninvasive ventilation failure in patients with AECOPD with preserved left ventricular function, but they did not assess the association of BNP and in-hospital mortality.^[13] Another previous retrospective study by Muhammad et al. demonstrated that log-transformed NT-pro-BNP levels were positively associated with echocardiographically estimated right ventricular systolic pressure; however, NT-pro-BNP was not associated with the need for noninvasive positive pressure ventilation/mechanical ventilation or with in-hospital mortality in patients with AECOPD without underlying left ventricular dysfunction.^[18]

Plasma brain natriuretic peptide and NT-pro-BNP are cardiac neurohormones that are synthesized and released from ventricular myocytes in response to myocardial stretch.^[4] It was established that NT-pro-BNP is a diagnostic and prognostic biomarker of congestive heart failure,^[5] and it has also been found to be a significant and independent predictor of death and cardiovascular events in stable coronary artery disease.^[6] In our study, we had excluded patients with a past medical history of coronary ischemic heart disease; however, we had not obtained the echocardiographic data; therefore, a small number of patients with undiagnosed heart failure may have been included. The meta-analysis performed by Pavasini et al. suggested that having a history of heart failure did not influence the relationship between elevated NT-pro-BNP levels and long-term mortality.^[18]

The pathophysiological processes underlying the elevation of BNP level in patients with exacerbations of COPD are unknown. Hypoxia often occurs in severe COPD, especially in patients with AECOPD. In our research, oxygen tension on arterial blood gas measurement was strongly associated with in-hospital mortality (P=0.008), composite outcome of in-hospital mortality or mechanical ventilation(P=0.009), and mechanical ventilation(P=0.014) in univariate analysis. Hypoxia can cause pulmonary hypertension and right ventricular dysfunction by pulmonary vasoconstriction.^[7] Concentration of NT pro-BNP was significantly higher in those with a higher pulmonary hypertension than in those with a lower pulmonary hypertension, and they found that NT pro-BNP was an excellent discriminator of right-ventricular impairment but not of cor pulmonale.^[8] Previous studies have found that BNP and NT-pro-BNP levels were elevated in patients with pulmonary thromboembolism, and BNP may be a useful determinant of the short-term outcome.^[9]

Coronary artery ischemia may be more likely to occur in patients with AECOPD. Gavin et al found that exacerbations of COPD increase the risk of myocardial infarction.^[14] This finding may be related to hypoxic ischemia of myocardium caused by hypoxia. Hypoxic myocardial ischemia leads to a decrease in myocardial contractility, which increases the burden on the heart and increases BNP or NT-pro-BNP secretion. In our study, 12 patients had acute myocardial infarction during hospitalization and were excluded.

There are some limitations to our research. First, our study was observational; no causal inference can be obtained, and relationships should be interpreted as associations. Second, COPD specific diagnostic codes for the identification of patients were adopted. Spirometry data of some patients were not available completely. However, we reviewed the electronic patient files and medical data intelligence platform of Jinan Central Hospital and found that they were hospitalized many times and inhaled maintenance drugs of COPD for a long time; in subgroup analysis, irrespective of whether data on the lung function were missing or not, the results were consistent. Third, although our study was a retrospective single-center trial, it was closer to real-world clinical practice, and the patient treatments by clinicians were not influenced by the study. Considering that no multicenter study has been performed so far, a multi-center prospective study is urgently needed to further explore the prognostic efficiency of BNP for AECOPD.

Table 4 Unadjusted hazard ratios for log₂BNP and in-hospital mortality, composite of in-hospital mortality or invasive ventilation, invasive ventilation by subgroups

	No. of patients	Mortality HR (95% CI)	<i>P</i> interaction	Mortality or invasive ventilation HR (95% CI)	<i>P</i> interaction	Invasive ventilation HR (95% CI)	<i>P</i> interaction
Sex			0.051		0.377		0.173
female	110	1.30 (0.83, 2.06)		1.45 (1.05, 1.98)		1.43(1.03, 1.99)	
male	190	2.60 (1.64, 4.11)		1.54 (1.18, 2.01)		1.71(1.27, 2.31)	
FEV1 (% predicted)			0.915		0.676		0.989
missing	142	1.97 (1.32, 2.94)		1.41 (1.12, 1.79)		1.52 (1.17, 1.98)	
No missing	158	2.133 (1.19, 3.82)		1.54 (1.02, 2.32)		1.54 (1.02, 2.32)	
Age, years			0.218		0.809		0.794
low	134	2.43 (1.10, 5.35)		1.37 (1.08, 1.74)		1.41(1.09, 1.83)	
high	166	1.77 (1.26, 2.48)		1.60 (1.21, 2.12)		1.68 (1.25, 2.27)	

Conclusions

This study suggests that a higher log₂BNP value was significantly associated with in-hospital mortality and invasive mechanical ventilation in patients with AECOPD, and BNP is a promising prognostic marker of in-hospital mortality and invasive mechanical ventilation in patients with AECOPD. These findings justify that a multi-center prospective study is urgently needed to further explore the prognostic efficiency of BNP for AECOPD.

Abbreviations

AECOPD, Acute exacerbations of chronic obstructive pulmonary disease; BAP65, BUN level > 25 mg/dL, Altered mental status, Pulse > 109 beats/min, Age ≥ 65 years; BNP, B-type natriuretic peptide; COPD, Chronic obstructive pulmonary disease; CURB65, Confusion, Urea > 7mmol/L, Respiratory rate ≥ 30/min, Blood

pressure systolic < 90 mmHg or diastolic <60 mmHg and age > 65 years; ICD-9, International Statistical Classification of Diseases and Related Health Problems, Ninth Revision; ICU, Intensive care unit; SD, Standard deviation

Declarations

Ethics approval and consent to participate

Ethics Committees of Jinan Central Hospital reviewed and approved this retrospective study protocol.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jiyun Cui conceived and designed the study; Jiyun Cui and Jie Liu devised the analysis of the data. Jiyun Cui, Jing Wang, Meng Lv, Chunyan Xing and Yanbiao Chu performed the study and drafted the manuscript. Jiyun Cui proofed the manuscript.

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Not Applicable.

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Figures

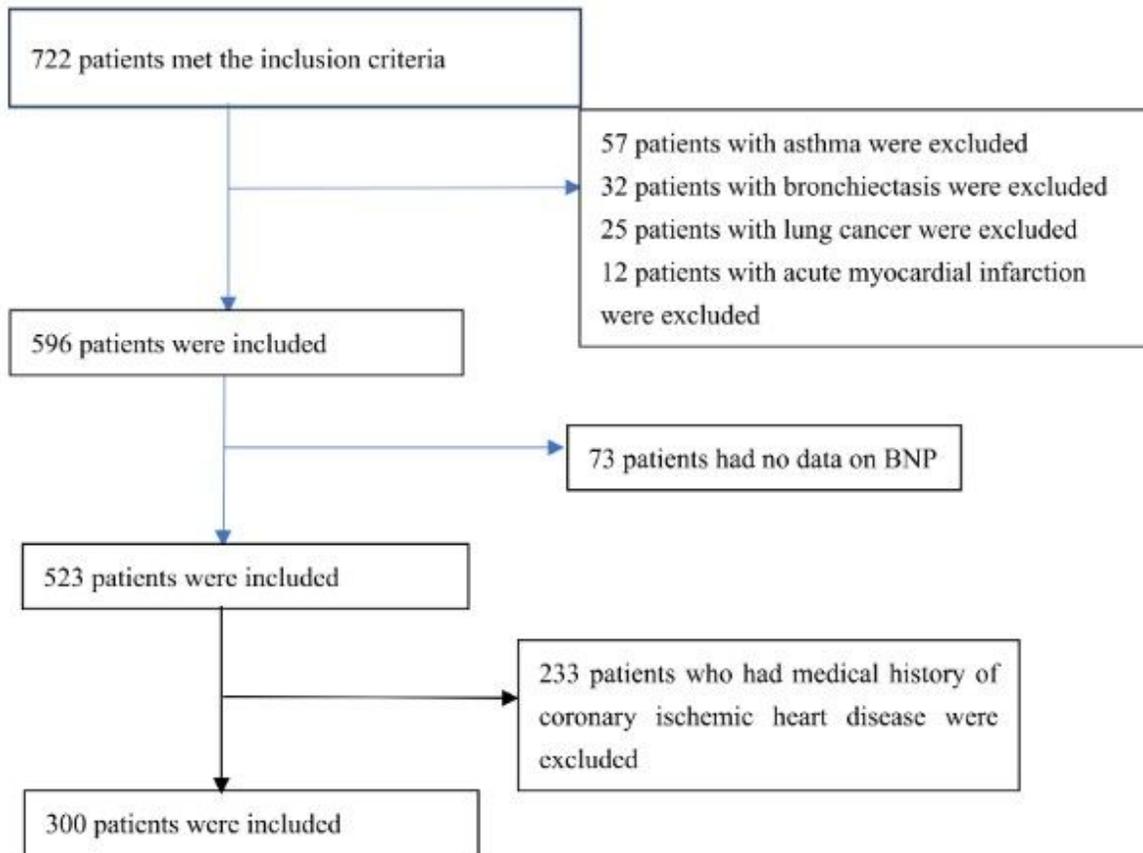


Figure 1

Flowchart of patient selection

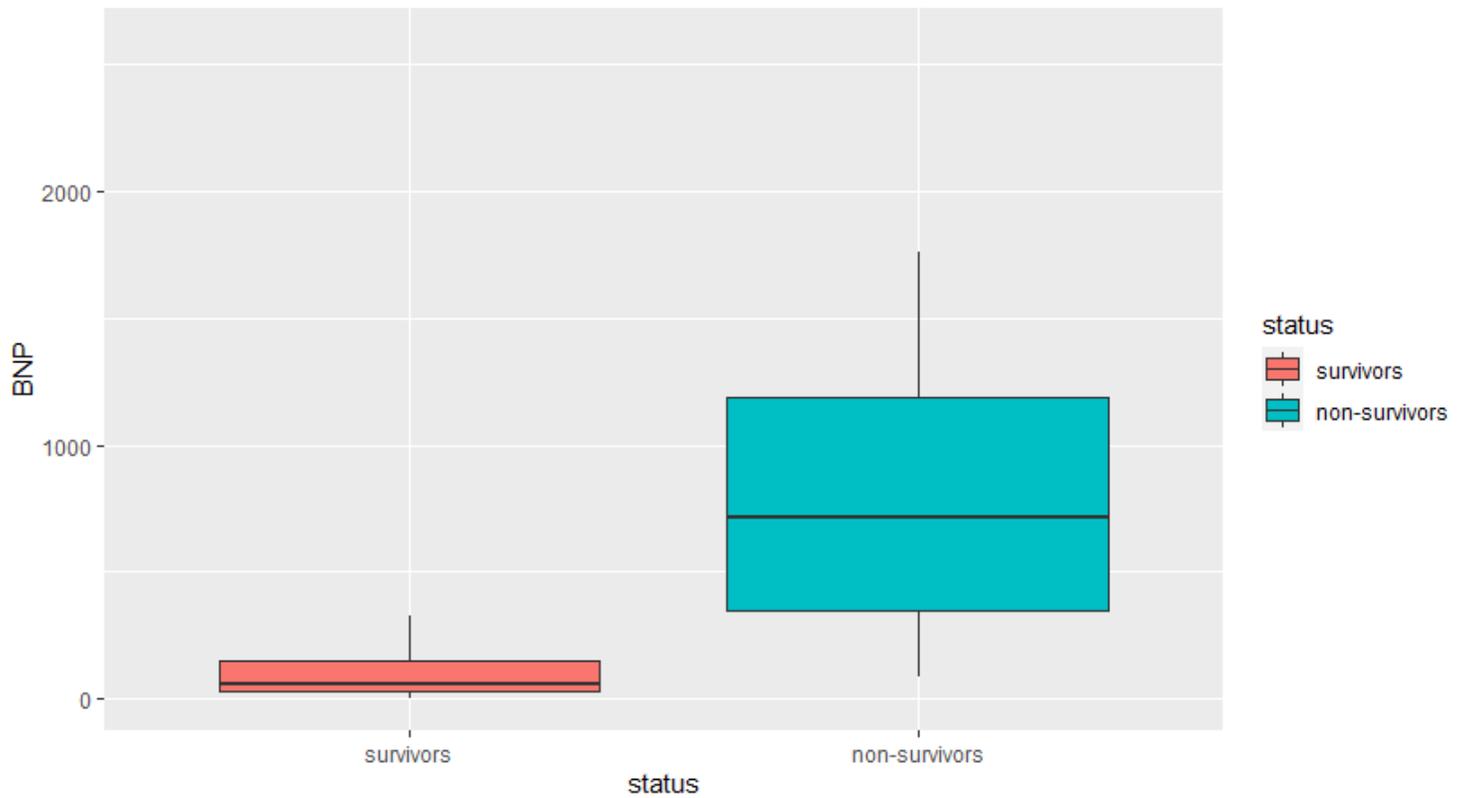


Figure 2

BNP levels in non-survivors and survivors

Supplementary Files

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