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Combining the use of amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the prognosis of hospitalized heart failure patients

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ABSTRACT

Objective: To investigate whether the combination of measuring amino-terminal pro-B-type natriuretic peptide (NT-proBNP) and B-type natriuretic peptide (BNP) could provide additional prognostic value in hospitalized heart failure patients.

Methods: We measured both BNP and NT-proBNP simultaneously at baseline in 1464 hospitalized heart failure patients who were admitted to our heart failure center. All patients were followed-up with the median follow-up period of 533 days. The primary endpoint is a composite of all-cause death (non-transplantation patients) or heart transplantation.

Results: The median molar ratio of NT-proBNP/BNP was 2.37, but the range of the molar ratio varied from 1.57 to 3.75 (lower quartile to higher quartile). Using the cut-off value of 1790 pg/mL for NT-proBNP and 495 pg/mL for BNP from the ROC curve analysis, univariate Cox proportional regression analysis showed that the low/high group (NT-proBNP < 1790 pg/mL and BNP ≥ 495 pg/mL), high/low group (NT-proBNP ≥ 1790 pg/mL and BNP < 495 pg/mL) and high/high group (NT-proBNP ≥ 1790 pg/mL and BNP ≥ 495 pg/mL) had significant higher risk of all-cause death or heart transplantation [HR (hazard ratio): 2.87, 95% CI (confidence interval): 1.69–4.89, $p < .001$; HR: 2.68, 95% CI: 1.91–3.76, $p < .001$; HR:5.07, 95% CI: 3.85–6.67, $p < .001$] than low/low group (NT-proBNP < 1790 pg/mL and BNP < 495 pg/mL). In turn, the high/high group had higher risk of all-cause death or heart transplantation than low/high (HR: 1.70, 95% CI: 1.04–2.80, $p = .035$) and high/low groups (HR: 1.88, 95% CI: 1.42–2.49, $p < .001$). The low/high and high/low groups had a similar risk of all-cause death or heart transplantation. Further multivariable Cox regression analysis also showed that both BNP and NT-proBNP above the cut-off values independently predicted the worst prognosis, while either one of the two biomarkers above the cut-off value indicated the moderate poor prognosis and both below the cut-off values indicated the best prognosis (p for trend < 0.001).

Conclusion: The plasma levels of NT-proBNP and BNP do not always increase proportionally in heart failure patients. The combination of testing NT-proBNP and BNP may add prognostic value to predict adverse events in hospitalized heart failure patients.

1. Introduction

B-type natriuretic peptide (BNP) and amino-terminal pro-B type natriuretic peptide (NT-proBNP) are the most widely used and recommended biomarkers of prognosis and for diagnosis of heart failure [1–4]. They are degraded from the prohormone pro-B-type natriuretic peptide (proBNP) and released from cardiomyocytes in response to mechanical or neurohormonal stimulation [5,6]. The proteolytic cleavage of the proBNP produces the biological functional BNP and inactive NT-proBNP in a 1:1 M ratio.

However, the plasma level of NT-proBNP is generally higher than BNP. The two peptides are different in biological half-life and clearance [7]. BNP is removed from the circulation faster than NT-proBNP (half-life of 20 vs. 120 min) [8,9]. NT-proBNP clearance is more influenced by the renal function than BNP [10,11]. Besides, BNP is also removed by binding to the natriuretic peptide receptor type C (NPR−C) and by

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neprilysin, etc. BNP is less stable than NT-proBNP if blood samples are collected in the glass tubes than in the PET tubes [12]. In addition, there are significant differences in analytical characteristics and measured values among the most popular commercial methods for BNP and NT-proBNP [13].

In most clinical practice, we measured either BNP or NT-proBNP, and we consider the two biomarkers to be of the same significance [1,14]. However, we observed that NT-proBNP and BNP do not always change in the same direction in heart failure patients, and BNP and NT-proBNP could not be interchanged with each other. The exact relationship between NT-proBNP and BNP and its clinical significance is still unknown.

In this retrospective study, we examined the baseline clinical factors that might be associated with the distribution of NT-proBNP and BNP and investigate whether the combination of NT-proBNP and BNP could provide additional prognostic information in hospitalized heart failure patients.

2. Methods

2.1. Study patients

This study retrospectively recruited hospitalized heart failure patients who were admitted to the Heart Failure Center of Fuwai Hospital (Beijing, China) from March 2009 and March 2016. At least two cardiologists confirmed Patients' diagnoses according to the guidelines [1,2]. Patients with both BNP and NT-proBNP measured at admission were finally enrolled. Patients were prescribed with guideline-directed medical therapy if they could tolerate the medication during hospitalization and after discharge.

The exclusion criteria included acute myocardial infarction, acute myocarditis, infectious endocarditis, constrictive pericarditis, pericardial effusion, pulmonary thromboembolism and severe respiratory diseases, aortic dissection, malignancy, prior heart transplantation or mechanical circulatory assist device, end-stage renal disease required dialysis and other severe infectious or systemic diseases.

This study was conducted under the principles contained in the Declaration of Helsinki and the ethical standards of the institutional and national research committee. Each participant had signed the informed consent in this study.

2.2. Data collection

Blood samples were taken in the fasting status at baseline, including BNP, NT-proBNP, routine blood tests, and biochemical parameters. Blood samples were collected strictly following a standard procedure and were sent to the laboratory for immediate testing using standard techniques. Plasma BNP (Triage MeterPro Chemistry Analyzer, Biosite Inc., San Diego, US) and plasma NT-proBNP (PATHFAST ® POC test, Mitsubishi Chemical Europe GmbH, Germany) were measured by commercially available assays, both of which have acceptable precision and coefficient of variation [15–17]. We transformed the unit of BNP and NT-proBNP from pg/mL to pmol/L using the molecular weights of BNP (3464) and NT-proBNP (8460) when appropriate. Estimated glomerular filtration rate (eGFR) was calculated by the modified MDRD equation for Chinese population [18]. We performed echocardiography in all the patients during hospitalization. Measurement of cardiac structures and the left ventricular ejection fraction (LVEF) was performed by commercially available ultrasound systems according to the established method by echocardiologists. We defined the patients as heart failure with reduced ejection fraction (HFrEF) when EF < 40%, heart failure with middle-range ejection fraction (HFmrEF) when 40% ≤ EF < 50%, and heart failure with preserved ejection fraction (HFpEF) when EF ≥ 50% [1,2].

2.3. Follow-up and primary endpoints

The primary endpoint was a composite of all-cause death or heart transplantation. When the heart transplantation was performed in a patient, the endpoint event was counted, and the patient will not be followed up for death. Follow-ups were done either by telephone or clinical visits at 3rd month, 6th month, 12th month and every 6 months after that. We got the information about the death or heart transplantation event from the patients themselves, their families and their affiliated hospitals.

2.4. Statistical analyses

Continuous values with normal distribution were expressed as the mean ± standard deviation (SD), whereas data with skewed distribution were expressed as the median (interquartile range). Categorical variables were expressed as the number, n (proportions, %). For continuous variables with skewed distribution, Mann-Whitney *U* test was performed for comparison of each two groups. For categorical variables, the $\chi 2$ test was used for comparison.

BNP and NT-proBNP were expressed as $\log_{10}$-transformed (lg) data in correlation or linear regression analyses. The correlation between baseline concentrations of BNP and NT-proBNP was assessed using Pearman's correlation coefficient. Multiple linear regression analysis with stepwise method was used to identify the independent clinical factors correlated with baseline concentrations of BNP and NT-proBNP.

Survival curves for all-cause death or heart transplantation event were determined using the Kaplan-Meier method. Survival curves were compared between two or three groups with the log-rank test, as appropriate. A univariate Cox proportional hazards regression analysis was performed to identify predictors of end-points, and then multivariable analysis with the Forward: LR method proceeded. Variables with significant *p* values ($p < .05$) were retained in the final multivariable model. We constructed the receiver operating characteristic (ROC) curves for BNP and NT-proBNP to predict all-cause death or heart transplantation. The area under the curve (AUC) was calculated, and we defined a value from the upper left corner of the ROC curve of NT-proBNP or BNP as the best cut-off value for the future all-cause death or heart transplantation event. All statistical analyses were performed using the SPSS (version 22; IBM) and R language version 3.5.1 (www.r-project.org). All tests were made at a 2-sided, 5% significance level.

3. Results

3.1. Baseline clinical characteristics

A total of 1464 patients were finally enrolled in this study. The median age of the patients was 58 years old. The percentage of male patients was 72.7%. The percentage of coronary artery disease (CAD) was 36.1%, dilated cardiomyopathy (DCM) 27.2%, and the other non-ischemic heart failure 36.7%. The median values of BNP, NT-proBNP and molar ratio of NT-proBNP/BNP were 375.0 pg/mL, 2028.8 pg/mL and 2.37, respectively. The distribution of the molar ratio of NT-proBNP/BNP was wide as shown in Fig. 1.

We divided patients into two groups based on the median value of the molar ratio of NT-proBNP/BNP. The clinical characteristics of the whole population and the subgroups were shown in Table 1. The patients with high molar ratio of NT-proBNP/BNP tended to be older, and had higher level of systolic blood pressure (SBP) and NT-proBNP at admission, but lower eGFR, left ventricular diameter in diastole (LVDD), BNP and other biochemical parameters such as hemoglobin (Hb), hematocrit (Hct), total bilirubin (TB), direct bilirubin (DB), and low-density lipoprotein-cholesterol (LDL-C). The percentage of female, history of atrial flutter (AF) or atrial fibrillation (Af), and HFpEF were higher in the high molar ratio group.

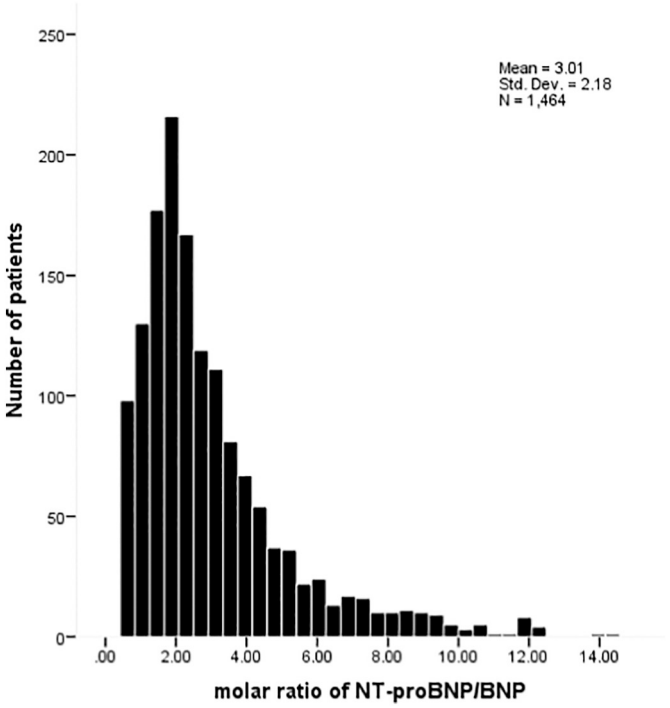

Fig. 1. Distribution of molar ratio of NT-proBNP/BNP.

3.2. Correlates of BNP and NT-proBNP

The baseline concentrations of lgBNP and lgNT-proBNP were strongly correlated with each other ($r = 0.851$, $p < .001$) (Fig. 2).

Correlation analysis showed that the parameters of body mass index (BMI), heart rate at admission, SBP at admission, left atrial anteroposterior diameter (LAD), LVDD, LVEF, eGFR, and NYHA class were all correlated with lgNT-proBNP and lgBNP. LgNT-proBNP were also correlated with age and presence of atrial fibrillation/flutter. Parameters of age, the presence of atrial fibrillation/flutter, heart rate at admission, LVDD, LVEF, and eGFR were correlated with the molar ratio of NT-proBNP/BNP.

Multivariable linear regression analyses (stepwise method) further showed that BMI, heart rate at admission, LAD, LVEF, eGFR and NYHA class were independently correlated with lgNT-proBNP level ($p < .001$) and lgBNP level ($p < .001$) in heart failure patients. Presence of atrial fibrillation/flutter was also independently correlated with lgNT-proBNP ($p = .024$). Presence of AF/Af, LVEF, and eGFR were independently correlated with the molar ratio of NT-proBNP/BNP. Association analysis was shown in Table 2.

3.3. BNP and NT-proBNP as the prognostic markers for all-cause death or heart transplantation

Among the 1464 patients, 136 were lost during the follow-up. The rate of follow-up was 90.7%. The median follow-up period was 533 days for the study patients (lower and upper quantiles: 241–1014 days). Of the 1328 patients, 335 developed death, 28 underwent heart transplantation, 249 were rehospitalized, and 716 patients survived free of any event during the follow-up period.

Univariate Cox regression analysis showed that both NT-proBNP and BNP were risk factors for all-cause death or heart transplantation in heart failure patients, the higher the NT-proBNP and BNP (per 1 pmol/L), the higher the event rate [HR (hazard ratio) = 2.13, 95% CI (confidence interval) 1.88–2.4, $p < .001$; HR = 5.76, 95% CI 4.44–7.48, $p < .001$, respectively]. Multivariable Cox regression analysis including the other covariables of age, BMI, SBP at admission, NYHA class, LAD, LVDD, LVEF, TB, DB, uric acid (UA), eGFR, and Hb, showed that both NT-proBNP and BNP were independent risk factors for all-cause death or heart transplantation event in heart failure patients (Table 3).

3.4. ROC curve analysis to predict all-cause death or heart transplantation event

ROC curves were constructed to compare the ability of NT-proBNP and BNP to predict all-cause death or heart transplantation. NT-proBNP and BNP could significantly predict the occurrence of all-cause death or heart transplantation (AUC: 0.69, 95% CI: 0.66–0.73, $p < .001$; AUC: 0.71, 95% CI: 0.67–0.74, $p < .001$. respectively). The AUC between NT-proBNP and BNP were not significantly different for predicting all-cause death or heart transplantation in heart failure patients ($p = .276$) (Fig. 3). The sensitivity and specificity of the nearest value (1790 pg/mL) of NT-proBNP from the upper left corner of the ROC curve to predict all-cause death or heart transplantation were 76.1%, and 55.1%, respectively. The sensitivity and specificity of the nearest value (495 pg/mL) of BNP were 62.5%, and 68.2%, respectively.

Using them as the cut-off values, Kaplan-Meier analysis showed a significantly lower probability of all-cause death or heart transplantation over time in the patients with lower NT-proBNP or lower BNP during the follow-up period ($p < .001$) (Fig. 4). Patients were stratified into 4 groups based on the combination of the cutoff values of NT-proBNP (1790 pg/mL) and BNP (495 pg/mL): low/low group (NT-proBNP < 1790 pg/mL and BNP < 495 pg/mL); low/high group (NT-proBNP < 1790 pg/mL and BNP ≥ 495 pg/mL), high/low group (NT-proBNP ≥ 1790 pg/mL and BNP < 495 pg/mL) and high/high group (NT-proBNP ≥ 1790 pg/mL and BNP ≥ 495 pg/mL). Kaplan-Meier analyses showed that the risk of adverse events was the lowest in the low/low group than the other three groups($p < .001$). There was no difference between the high/low and low/high groups in prognosis (Fig. 5).

Univariate Cox proportional hazards analysis showed that the risk of all-cause death or heart transplantation was the highest in the high/high groups (HR:5.07, 95% CI: 3.85–6.67, $p < .001$), and higher in the low/high and high/low groups (HR: 2.87, 95% CI: 1.69–4.89, $p < .001$; HR: 2.68, 95% CI: 1.91–3.76, $p < .001$; respectively), with low/low group as the reference. The high/high group had a higher risk of all-cause death or heart transplantation event as compared with low/high (HR: 1.70, 95% CI: 1.04–2.80, $p = .035$) and high/low groups (HR: 1.88, 95% CI: 1.42–2.49, $p < .001$).

Due to the similar prognosis between the high/low and low/high groups, we reclassified the groups as low/low group (NT-proBNP < 1790 pg/mL and BNP < 495 pg/mL, grade 0), either high NT-proBNP or BNP group (NT-proBNP ≥ 1790 pg/mL or BNP ≥ 495 pg/mL, grade 1) and high/high group (NT-proBNP ≥ 1790 pg/mL and BNP ≥ 495 pg/mL, grade 2). Multivariable Cox hazard analysis showed that after adjusting the covariables of age, BMI, SBP at admission, NYHA class, LAD, LVDD, LVEF, TB, DB, UA, eGFR, and Hb, NT-proBNP and BNP, the risk of adverse events increases with the grade according to the number of NT-proBNP or BNP above the cut-off value (HR = 1.35,1.22–1.51, p for trend < 0.001).

4. Discussion

In this study, we found that the baseline concentrations of BNP and NT-proBNP did not always increase proportionally. With the cut-off value of 1790 pg/mL for NT-proBNP and 495 pg/mL for BNP, the risk of all-cause death or heart transplantation increased with the grading classification according to the number of NT-proBNP or BNP above the cut-off value: low/low group (NT-proBNP < 1790 pg/mL and BNP < 495 pg/mL, grade 0), either high NT-proBNP or BNP group (NT-proBNP ≥ 1790 pg/mL or BNP ≥ 495 pg/mL, grade 1) and high/high group (NT-proBNP ≥ 1790 pg/mL and BNP ≥ 495 pg/mL, grade 2).

Table 1
Baseline clinical characteristics.

	All patients (n = 1464)	Low NT-proBNP/BNP molar ratio (< 2.37) (n = 732)	High NT-proBNP/BNP molar ratio (≥2.37) (n = 732)	p value
Age (years)	58 (47–69)	57 (46–67)	60 (48–70)	0.001
Male (n, %)	1065 (72.7%)	553 (75.5%)	512 (69.9%)	0.019
BMI (kg/m^2)	24.2 (21.6–26.8)	24.2 (21.7–27.0)	24.2 (21.6–26.7)	0.594
Hypertension (n, %)	712 (48.6%)	339 (46.3%)	373 (51.0%)	0.084
Diabetes mellitus (n, %)	462 (31.6%)	232 (31.7%)	230 (31.4%)	0.955
Hyperlipidemia (n, %)	517 (35.3%)	271 (37.0%)	246 (33.6%)	0.189
AF/Af (n, %)	505 (34.5%)	202 (27.6%)	303 (41.4%)	< 0.001
Smoking (n, %)	713 (48.7%)	372 (50.8%)	341 (46.6%)	0.117
Drinking (n, %)	514 (35.1%)	270 (36.9%)	244 (33.3%)	0.171
CAD (n, %)	529 (36.1%)	268 (36.6%)	261 (35.7%)	0.744
DCM (n, %)	398 (27.2%)	210 (28.7%)	188 (25.7%)	0.217
Distribution of NYHA class				0.971
NYHA class I (n, %)	18 (1.2%)	10 (1.4%)	8 (1.1%)	
NYHA class II (n, %)	300 (20.5%)	149 (20.4%)	151 (20.6%)	
NYHA class III (n, %)	715 (48.8%)	357 (48.8%)	358 (48.9%)	
NYHA class IV (n, %)	431 (29.4%)	216 (29.5%)	215 (29.4%)	
Distribution of HF classification				< 0.001
HFrEF (n, %)	844 (57.7%)	458 (62.6%)	386 (52.7%)	
HFmrEF (n, %)	231 (15.8%)	109 (14.9%)	122 (16.7%)	
HFpEF (n, %)	389 (26.6%)	165 (22.5%)	224 (30.6%)	
UA (umol/L)	446.4 (355.1–558.1)	444.8 (354.0–548.1)	447.8 (357.1–571.2)	0.569
eGFR (mL/min/1.73m^2)	93.1 (72.0–114.0)	96.4 (77.7–116.2)	88.9 (67.9–111.3)	< 0.001
Hb (g/L)	138 (123–152)	141 (126–153)	137 (119–151)	0.001
Hct (%)	41.2 (37.0–45.5)	41.9 (37.9–45.6)	40.8 (36.1–45.2)	0.001
TB (mmol/L)	20.2 (14.1–30.5)	21.7 (15–32.2)	19.4 (13.7–28.4)	< 0.001
DB (mmol/L)	4.1 (2.7–6.8)	4.4 (2.8–7.4)	3.8 (2.6–6.1)	0.002
LDL-C (mmol/L)	2.4 (1.9–3.0)	2.5 (2.0–3.1)	2.4 (1.8–3.0)	0.008
CRP (mg/L)	4.7 (2.5–9.6)	4.5 (2.5–9.3)	4.8 (2.4–10.1)	0.661
Heart rate (beats/min)	78 (66–90)	78 (68–91)	78 (65–90)	0.164
SBP (mmHg)	118 (104–131)	116 (103 − 130)	119 (105–133)	0.036
DBP (mmHg)	70 (62–80)	71 (64–80)	70 (61–80)	0.286
LAD (mm)	44 (39–50)	45 (40–50)	44 (39–50)	0.144
LVDD (mm)	62 (53–70)	63 (55–71)	61 (51–69)	0.001
LVEF (%)	35 (28–50)	35 (26–45)	38 (29–53)	< 0.001
BNP (pg/mL)	375.0 (149.3–772.0)	503.5 (250.0–946.3)	241.0 (100.5–561.8)	< 0.001
NT-proBNP (pg/mL)	2028.8 (944.6–4092.0)	1785.4 (870.0–3395.5)	2296.0 (1105.2–5272.8)	< 0.001
Molar ratio of NT-proBNP/BNP	2.37 (1.57–3.75)	1.57 (1.13–1.96)	3.74 (2.94–5.30)	< 0.001
ACEI/ARB (n, %)	849 (58.0%)	427 (58.3%)	422 (57.7%)	0.832
β-blocker (n, %)	1256 (85.8%)	632 (86.3%)	624 (85.2%)	0.600
MRA(n, %)	1049 (71.7%)	536 (73.2%)	513 (70.1%)	0.202
Oral diuretics (n, %)	1302 (88.9%)	655 (89.5%)	647 (88.4%)	0.560
Digoxin (n, %)	811 (55.4%)	423 (57.8%)	388 (53.0%)	0.074

ACEI, angiotensin-converting enzyme inhibitor; Af, atrial fibrillation; AF, atrial flutter; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CRP, C reactive protein; CAD, coronary artery disease; DB, direct bilirubin; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with middle-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Hb, hemoglobin; Hct, hematocrit; LAD, left atrial anteroposterior diameter; LDL-C, low density lipoprotein-cholesterol; LVDD, left ventricular diameter in diastole; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TB, total bilirubin; UA, uric acid.

The low/high NT-proBNP/BNP and high/low NT-proBNP/BNP groups were not different in predicting all-cause death or heart transplantation.

Initially, BNP and NT-proBNP were secreted from cardiomyocytes in 1:1 M ratio. Due to the biological characteristics, the range of NT-proBNP level has been shown to be wider than BNP [19]. Though NT-proBNP is generally higher than BNP, we expect them to change in the same direction proportionally. However, in our clinical practice, we found that the two biomarkers did not always simultaneously increase or decrease. The clinical significance of this phenomenon is still unclear. Indeed, previous studies have shown that BNP and NT-proBNP have some different features in detecting cardiac function. BNP may be a better indicator for the biochemical diagnosis of more severely impaired LVEF, while NT-proBNP might be a more discerning marker of early systolic left ventricular dysfunction [20,21]. The combination of the two biomarkers to optimally predict prognosis in patients with heart failure needs to be explored.

We measured the BNP and NT-proBNP levels simultaneously in 1464 hospitalized heart failure patients and examined whether the simultaneous measurement of both NT-proBNP and BNP provide additional prognostic information. It was found that the baseline concentrations of NT-proBNP and BNP were strongly correlated, in accordance with previous studies [22]. However, their change was not always proportional, with the molar ratio varying widely. Relative few studies reported this phenomenon except a recent Japanese study [23].

Patients with a different profile of BNP and NT-proBNP distributions had different clinical phenotypes. The patients with a high molar ratio of NT-proBNP/BNP tended to have lower eGFR. It might be explained that NT-proBNP was more influenced by renal function than BNP [24,25]. Older patients, female patient, patients with AF or Af, and HFpEF patients tended to have a higher molar ratio. These inferences about age and eGFR have also been reported by the aforementioned Japanese study. But this study is not in full agreement with our study with regards to its relationship with LVEF, because they found that patients with a high molar ratio of NT-proBNP/BNP had significantly lower LVEF than those with a low molar ratio, while our study showed the opposite trend [23]. The studied populations are distinctively different between the two studies. They recruited stable outpatients who visited the outpatient clinic with at least one cardiovascular risk factor,

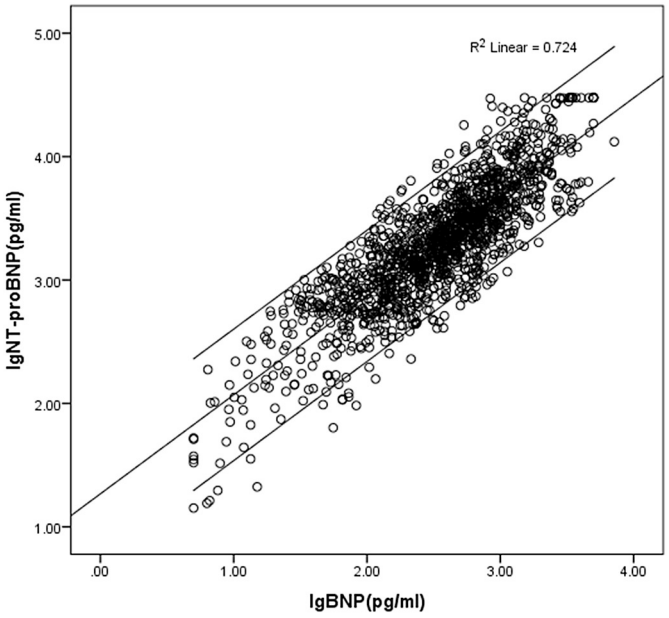

Fig. 2. Correlation between baseline concentrations of lgBNP and lgNT-proBNP.

while we enrolled the hospitalized patients with definite diagnosis of heart failure. The levels of BNP and NT-proBNP are significantly lower in the Japanese study than those in ours [BNP: 33.5 (14.3–80.4) pg/mL vs 375.0 (149.3–772.0) pg/mL; NT-proBNP: 135.0 (57.0–433.0) pg/mL vs 2028.8 (944.6–4092.0) pg/mL, respectively]. Besides the LVEF is generally normal in their study (LVEF: 61% ± 8%), while LVEF is below 50% in 73.4% of patients in our study [LVEF: 35 (28–50) %]. Taken together, it still needs to be confirmed further by a prospective study.

In this study, we did not find the independent correlation between age and BNP or NT-proBNP, which is not in accordance with the previous research [26]. They reported the age dependency of both BNP and NT-proBNP in 311 patients with chronic heart failure of NYHA functional class III/IV. Moreover, they demonstrated that the relative increase of BNP with age was significantly larger than the corresponding increase of NT-proBNP with age. In healthy subjects, the relation between age and BNP or NT-proBNP is in a positive correlation. However,

Table 3
Univariate and multivariate cox proportional hazards analysis to evaluate the BNP and NT-proBNP as the prognostic markers for all-cause death or heart transplantation.

Variable	Univariate analysis			Multivariable analysis		
	HR	95%CI	*p* value	HR	95%CI	*p* value
NT-proBNP (pmol/L)	2.13	1.88–2.40	< 0.001	1.86	1.60–2.16	< 0.001
BNP (pmol/L)	5.76	4.44–7.48	< 0.001	3.98	2.92–5.42	< 0.001

Adjusted by age, BMI, SBP at admission, NYHA class, LAD, LVDD, LVEF, TB, DB. UA, eGFR, Hb.
BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; DB, direct bilirubin; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HR, hazard ratio; LAD, left atrial anteroposterior diameter; LVDD, left ventricular diameter in diastole; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TB, total bilirubin; UA, uric acid.

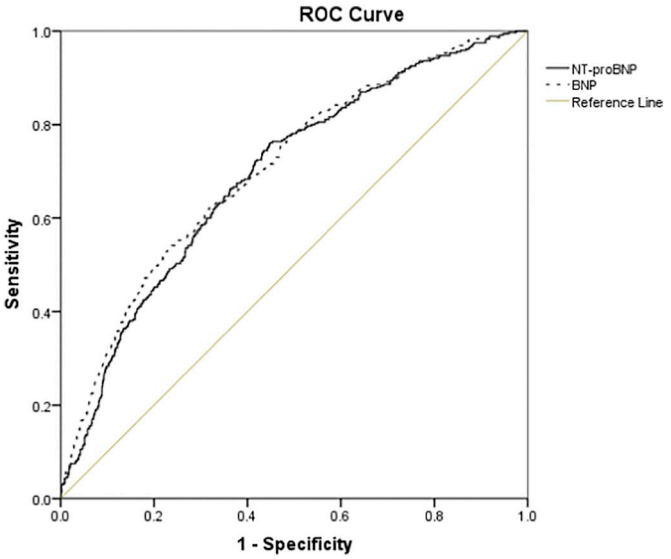

Fig. 3. ROC curves comparing the ability of NT-proBNP and BNP to predict all-cause death or heart transplantation. NT-proBNP: AUC: 0.69, 95% CI: 0.66–0.73, $p < .001$; BNP: AUC: 0.71, 95% CI: 0.67–0.74, $p < .001$.

Table 2
Clinical parameters associated with baseline lgBNP(pg/mL), lgNT-proBNP(pg/mL) and molar ratio of NT-proBNP/BNP.

Parameter	lgNT-proBNP				lgBNP				Molar ratio of NT-proBNP/BNP			
	Pearson analysis		Multiple linear regression		Pearson analysis		Multiple linear regression		Pearson analysis		Multiple linear regression	
	R	*p* value	β (SE)	*p* value	R	*p* value	β (SE)	*p* value	R	*p* value	β (SE)	*p* value
Age	0.069	0.008	–	–	0.019	0.461	–	–	0.088	0.001	–	–
Gender(male vs female)	−0.043	0.097	–	–	−0.014	0.582	–	–	−0.024	0.368	–	–
AF/Af	0.113	< 0.001	0.064 (0.028)	0.024	0.029	0.262	–	–	0.120	< 0.001	0.416 (0.122)	0.001
BMI	−0.234	< 0.001	−0.026 (0.003)	< 0.001	−0.199	< 0.001	−0.025 (0.003)	< 0.001	−0.046	0.081	–	–
Heart rate	0.156	< 0.001	0.004 (0.001)	< 0.001	0.176	< 0.001	0.004 (0.001)	< 0.001	−0.066	0.011	–	–
SBP	−0.170	< 0.001	–	–	−0.183	< 0.001	–	–	0.033	0.227	–	–
DBP	−0.047	0.087	–	–	−0.033	0.225	–	–	−0.023	0.400	–	–
LAD	0.198	< 0.001	0.007 (0.001)	< 0.001	0.197	< 0.001	0.009(0.001)	< 0.001	−0.027	0.305		
LVDD	0.167	< 0.001	–	–	0.216	< 0.001	–	–	−0.105	< 0.001	–	–
LVEF	−0.239	< 0.001	−0.006 (0.001)	< 0.001	−0.300	< 0.001	−0.009 (0.001)	< 0.001	0.129	< 0.001	0.016 (0.004)	< 0.001
eGFR	−0.224	< 0.001	−0.003 (0.000)	< 0.001	−0.162	< 0.001	−0.003 (0.000)	< 0.001	−0.087	0.001	−0.005 (0.002)	0.007
NYHA class	0.334	< 0.001	0.121 (0.018)	< 0.001	0.320	< 0.001	0.123 (0.019)	< 0.001	−0.004	0.891	–	–

Af, atrial fibrillation; AF, atrial flutter; BMI, body mass index; BNP, B-type natriuretic peptide; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; LAD, left atrial anteroposterior diameter; LVDD, left ventricular diameter in diastole; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SE, standard error.

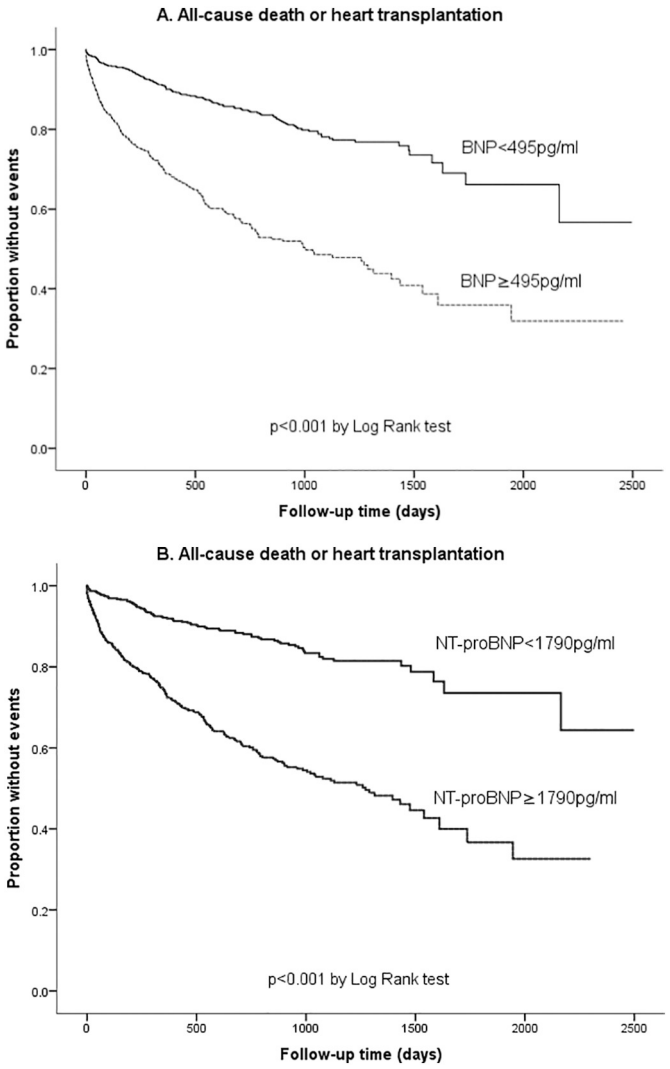

Fig. 4. Kaplan-Meier analysis for probability of all-cause death or heart transplantation. (a) Kaplan-Meier analysis showed a significantly lower probability of all-cause death or heart transplantation over time in the patients with BNP < 495 pg/mL during the follow-up period; (b) Kaplan-Meier analysis showed a significantly lower probability of all-cause death or heart transplantation over time in the patients with NT-proBNP < 1790 pg/mL during the follow-up period.

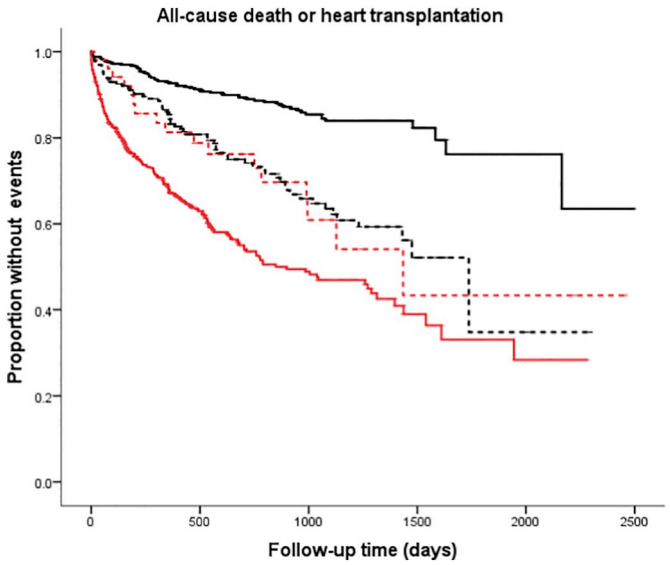

Fig. 5. Kaplan-Meier analyses showed that the risk of all-cause death or heart transplantation across the groups classified by NT-proBNP and BNP levels.
The risk of all-cause death or heart transplantation was the lowest in the low/low group than the other three groups($p < .001$). There was no difference between the high/low and low/high groups ($p = .77$). The high/high group had a higher risk of all-cause death or heart transplantation event as compared with high/low and low/high groups ($p < .001$ and $p = .033$, respectively).
The black solid line: low/low group (NT-proBNP < 1790 pg/mL and BNP < 495 pg/mL); the red dotted line: low/high group (NT-proBNP < 1790 pg/mL and BNP ≥ 495 pg/mL); the black dotted line: the high/low group (NT-proBNP ≥ 1790 pg/mL and BNP < 495 pg/mL); the red solid line: high/high group (NT-proBNP ≥ 1790 pg/mL and BNP ≥ 495 pg/mL).

though age is a major influential factor that should be considered during analysis, the other factor, especially the severity of heart failure, is more important in heart failure patients. In addition, the female gender is correlated with higher plasma BNP or NT-proBNP in healthy subjects, but not in the heart failure patients. These paradoxes in our study might be related to the imbalanced distribution of severity of heart failure in different age and gender groups. More importantly, it further indicates that BNP and NT-proBNP are more influenced by the severity of heart failure such as LVEF, LVDD or NYHA class, rather than the inherent factors of age and gender, indicating their advantage as the prognostic tools.

Though BNP and NT-proBNP had comparable ability to predict all-cause death or heart transplantation event in the present study, which is in accordance with a previous study [22,27], whether a combination of the two biomarkers could increase the prognostic value was unknown. There have been no definite cut-off points for NT-proBNP or BNP in prognosis [27]. The previous report showed that cut-off points associated with mortality ranged from 3001 to 17,860 pg/mL [27]. We used ROC curve to establish the cut-off points (1790 pg/mL for NT-proBNP and 495 pg/mL for BNP) and compared the subgroups in prognosis by combining BNP and NT-proBNP. It was found that patients with both higher levels of NT-proBNP and BNP had the worst prognosis, with one of them elevated in the middle, and both lower levels the best prognosis. Both BNP and NT-proBNP were affected by a series of clinical factors in the real world, such as renal function, BMI, and severity of heart failure [28,29]. Therefore, combining the two, especially when they do not proportionally change, is of significance. Our results suggest that simultaneous measurement of NT-proBNP and BNP may help identify hospitalized heart failure patients at high risk for all-cause death or heart transplantation event.

There are several clinical conditions when measurement of BNP is not appropriate. Because clearance of BNP is mediated by neprilysin, treatment with neprilysin inhibition via sacubitril/valsartan results in higher BNP level [30]. Another one is the infusion of recombinant human BNP, which lead to an increased circulatory level of BNP. In our study, these effects of the medication have been avoided.

Our study had some limitations. First, this is a retrospective observational study. Several clinical factors might affect the plasma level of BNP and NT-proBNP. Though both NT-proBNP and BNP were measured in a standardized way and the results from this study reflect the real-world condition, a prospective observational study is required to establish the exact relationship between the two parameters. Secondly, the precise mechanism of the mismatched values of BNP and NT-proBNP is unknown. This present study paved the way and brought up with the phenomenon, but it could not explain the mechanism. Thirdly, this study only compared the level of BNP and NT-proBNP at admission. Further research is required to assess their levels by serial measurements, to observe the changes following admission and discharge, which might unveil their relationship in heart failure patients more deeply. Finally, this study did not evaluate the economic efficiency for simultaneous measurement of both BNP and NT-proBNP.

Disclosure

The authors have no conflicts of interest to disclose.

Human subjects/informed consent statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union of Medical College) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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