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Value of N-terminal pro-brain natriuretic peptide and aortic diameter in predicting in-hospital mortality in acute aortic dissection

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ABSTRACT

Objective: To determine the value of N-terminal pro-brain natriuretic peptide (NT-proBNP) and aortic diameter in predicting in-hospital mortality in acute aortic dissection (AD).
Methods: A single-center prospective study was designed in the setting of University hospital in China. 122 patients with acute AD were enrolled. Admission plasma NT-proBNP levels and aortic diameter were measured.
Results: Plasma NT-proBNP concentrations ($P < 0.001$), aortic diameter ($P = 0.002$), and admission systolic blood pressure (SBP) ($P = 0.011$) were significantly increased in patients who died compared to those who survived during hospitalization. Furthermore, aortic diameter had positive correlations with NT-proBNP levels ($r = 0.270$, $P = 0.003$) and admission diastolic blood pressure (DBP) ($r = 0.202$, $P = 0.025$), respectively. Multiple logistic regression analysis demonstrated that NT-proBNP ≥569.75 pg/ml and aortic diameter ≥40 mm were strongly associated with in-hospital mortality. The odds ratio (OR) and 95% confidence interval (CI) were 3.246, 1.212–8.693 ($P = 0.019$); and 2.917, 1.102–7.722 ($P = 0.031$), respectively. Moreover, when NT-proBNP ≥1325.6 pg/ml, the sensitivity and specificity of NT-proBNP in predicting in-hospital mortality risk were 55.2% and 95.7% (95% CI, 0.707–0.891; $P < 0.001$), respectively. In addition, when aortic diameter ≥47 mm, the sensitivity and specificity were 58.6% and 88.2% (95% CI, 0.607–0.841; $P < 0.001$), respectively.
Conclusions: NT-proBNP ≥569.75 pg/ml and aortic diameter ≥40 mm were important risk factors and independently associated with acute AD in-hospital mortality. NT-proBNP ≥1325.6 pg/ml or aortic diameter ≥47 mm showed higher specificity in predicting in-hospital mortality. Using NT-proBNP and aortic diameter together showed better performance in predicting in-hospital mortality with higher sensitivity.

1. Introduction

Acute aortic dissection (AD) is a life-threatening cardiovascular disorder with high mortality. High mortality is commonly caused by severe complications including rupture of AD or aneurysm, cardiac tamponade, acute myocardial infarction, pleural effusion, or acute renal failure and so on [1]. Although imaging techniques modalities, and proper surgical or medical treatments are performed in diagnosing and treating AD, the misdiagnosis and in-hospital mortality rate still remain high [2,3]. The overall in-hospital mortality of acute AD was approximately 27% [4]. Furthermore, at present, no suitable biomarkers have been reported to predict in-hospital mortality effectively in acute AD.

N-terminal pro-brain natriuretic peptide (NT-proBNP) was a polypeptide neurohormone synthesized in ventricular myocardium, stimulated by ventricular volume expansion, overload vascular pressure and inflammation [5]. Elevated BNP concentrations were observed in critically ill patients, as well as in AD. BNP had been used in assessing cardiac hemodynamics and prognosis in hospitalized patients, and considered as a powerful independent predictor of all-cause and cardiovascular mortality [6–10].

However, there is still a lack of systematic research about whether NT-proBNP could provide valuable clinical prediction information for in-hospital short-term mortality in acute AD. Accordingly, the aim of this present study was to assess the admission plasma levels of NT-proBNP and aortic diameter in acute AD, and illustrate their values in predicting in-hospital mortality.

2. Materials and methods

2.1. Study population

One hundred and twenty-two consecutive patients with diagnosis of

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acute AD were recruited. Among these 122 patients, 93 patients survived and 29 died during hospitalization. We divided the patients into two groups (survival and death). Informed consent was obtained from all the patients for participation in this present study, according to the protocol approved by the Committee on Human Investigation at our institution.

2.2. Definitions

The diagnosis of AD was confirmed in all patients by history, chest radiography, transthoracic or transesophageal echocardiography, contrast-enhanced computed tomography. We classified AD according to Stanford classification [1]. AD was characterized by acute and chronic phase. The dissection was considered as acute AD if the time from the onset of the symptoms to admission was within 14 days, while chronic AD was that over 14 days [4]. Hypertension was established by a clinic record of systolic blood pressure ≥140 mmHg, and/or diastolic blood pressure ≥90 mmHg, or the use of antihypertensive agents. Diabetes mellitus (DM) was defined as treatment with oral hypoglycemic agents or insulin, or fasting glucose level ≥126 mg/dL, or a glycosylated hemoglobin A1c ≥6.5%. Smoking status was defined when the subjects were current smokers according to self-report. Marfan syndrome was diagnosed by the Ghent criteria. Glomerular filtration rate ≤60 ml/mim was defined as impaired renal function. The definitions of the above clinical variables associated with this study were similar to our previous study [11].

2.3. Serum measurements

Venous blood was drawn from all patients in a fasting state after admission (within 48 h after onset without pre-medications) before surgery. Plasma were obtained after rapidly centrifugation and were immediately stored at −20 °C for further analysis. Plasma NT-proBNP on admission was measured by using ELISA technique. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) were determined by standard quantitative assay techniques in the hospital Clinical Laboratory Center according to the manufacturers' instructions. All assays were run in duplicate.

2.4. Statistical analysis

Continuous variables were compared by means of *t* test for normally distributed data, nonparametric Mann-Whitney test for abnormally distributed data. Categorical variables were compared by chi-square test or Fisher's exact test. Correlations were assessed using Spearman's rank correlation. Univariate analysis and multiple logistic regression analysis were used to simultaneously analyze the influence of multiple factors on a variable. Receiver operating characteristic (ROC) analysis was performed to determine the cut-off value for NT-proBNP and aortic diameter to predict in-hospital mortality with high sensitivity and specificity. P-value < 0.05 were considered statistically significant. Data analysis was performed using a commercially available statistical software package (SPSS II for windows, version 18.0, Chicago, IL, USA).

3. Results

3.1. Plasma levels of biomarkers

Among the 122 patients with acute AD, 93 patients survived and 29 died during hospitalization. In this study, aortic diameter (46.0 ± 8.1 vs. 39.5 ± 6.5 mm, P = 0.002), admission systolic blood pressure (SBP) (185.0 ± 31.9 vs. 168.4 ± 25.6 mmHg, P = 0.011) and plasma NT-proBNP concentrations (1677.7 ± 1169.9 vs. 664.8 ± 461.6 pg/ml, P < 0.001) were significantly increased in patients who died compared to those who survived (Table 1) (Fig. 1) (Fig. 2).

Table 1
Baseline clinical characteristics of patients with acute AD.

Clinical variables	Survival	Death	P value
Number	93	29	—
Age (year)	49.4 ± 8.3	52.1 ± 8.5	0.174
Males, n (%)	77 (82.8)	26 (89.7)	0.559
History of smoking, n (%)	49 (52.7)	19 (65.5)	0.225
History of hypertension, n (%)	71 (76.3)	25 (86.2)	0.257
History of DM, n (%)	24 (25.8)	8 (27.6)	0.849
Type A AD, n (%)	54 (58.1)	22 (75.9)	0.084
Admission SBP (mmHg)	168.4 ± 25.6	185.0 ± 31.9	0.011
Admission DBP (mmHg)	97.7 ± 11.1	100.7 ± 12.5	0.300
Aortic diameter (mm)	39.5 ± 6.5	46.0 ± 8.1	0.002
Medications before admission, n (%)			
Aspirin	38 (40.9)	14 (48.3)	0.481
Nitroglycerin	31 (33.3)	12 (41.4)	0.428
Serum measurements			
NT-proBNP (pg/ml)	664.8 ± 461.6	1677.7 ± 1169.9	< 0.001
TC (mmol/L)	4.9 ± 0.9	4.8 ± 1.2	0.459
TG (mmol/L)	1.2 ± 0.6	1.0 ± 0.7	0.051
HDL-C (mmol/L)	1.1 ± 0.3	1.2 ± 0.3	0.345
LDL-C (mmol/L)	2.6 ± 1.1	2.8 ± 1.3	0.360
Time from admission to death (day)	—	3.8 ± 2.3	—

DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, Triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

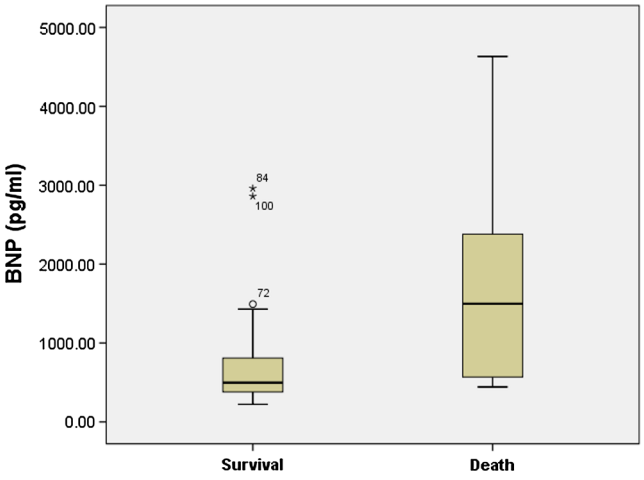

Fig. 1. Comparison of NT-proBNP between survival and patients who died.

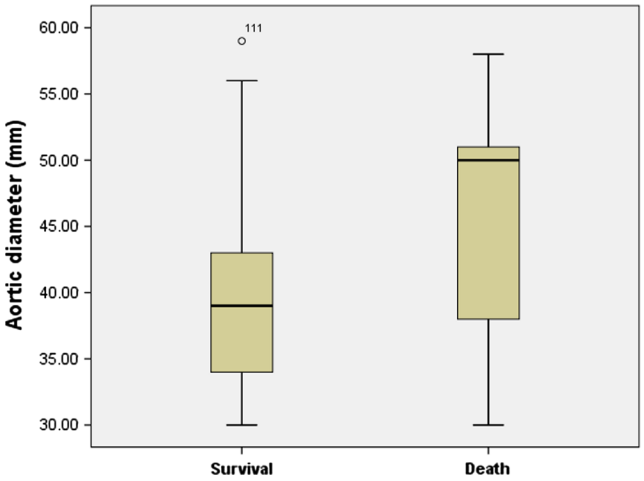

Fig. 2. Comparison of aortic diameter between survival and patients who died.

Table 2
Univariate analysis for in-hospital mortality.

Clinical variables	95% CI	P value
Age	0.989–1.092	0.131
Male	0.150–2.060	0.379
History of smoking	0.717–4.061	0.227
History of hypertension	0.608–6.170	0.264
History of DM	0.429–2.797	0.849
Type of AD	0.171–1.133	0.089
Admission SBP	1.006–1.037	0.007
Admission DBP	0.986–1.060	0.226
Aortic diameter	1.063–1.207	< 0.001
Aspirin	0.585–3.121	0.482
Nitroglycerin	0.600–3.321	0.430
NT-proBNP	1.001–1.002	< 0.001
TC	0.561–1.342	0.523
TG	0.302–1.121	0.106
HDL-C	0.496–8.695	0.317
LDL-C	0.803–1.604	0.472
Onset of symptoms to hospital admission (h)	0.929–1.018	0.227
Surgical treatment	0.593–3.167	0.461
Time of surgery (h)	0.939–1.022	0.344

DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, Triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval

3.2. Correlation analysis

Positive correlations were observed between plasma NT-proBNP levels and aortic diameter (r = 0.270, P = 0.003); as well as aortic diameter and admission diastolic blood pressure (r = 0.202, P = 0.025). Plasma NT-proBNP levels had no relationships with neither the time after onset nor the type of AD.

3.3. Univariate analysis and multiple logistic regression analysis for in-hospital mortality

The data demonstrated that age, type of AD, admission SBP, aortic diameter, NT-proBNP, and triglyceride (TG) with P-value about 0.1 in univariate analysis (Table 2). We calculated the median of the continuous data of age (50 years), admission SBP (179 mmHg), aortic diameter (40 mm), NT-proBNP (569.75 pg/ml), and TG (1.255 mmol/L). After putting these 6 variables into multiple logistic regression analysis, this study showed that NT-proBNP ≥569.75 pg/ml (OR, 3.246; 95% CI, 1.212–8.693; P = 0.019) and aortic diameter ≥40 mm (OR, 2.917; 95% CI, 1.102–7.722; P = 0.031) were significantly associated with in-hospital mortality (Table 3). Furthermore, by AD type stratification analysis, no significant associations were showed between the observed clinical variables and in-hospital mortality in either type A or type B AD.

3.4. Sensitivity and specificity of NT-proBNP and aortic dissection in predicting in-hospital mortality

We performed ROC analysis to determine the cut-off value of NT-proBNP and aortic diameter in predicting in-hospital mortality. The cut-off values were 1325.6 pg/ml for NT-proBNP, and 47 mm for aortic diameter. The areas under the curve (AUC) were 0.799 and 0.724 for NT-proBNP and aortic diameter, respectively (Table 4) (Fig. 3). Moreover, combining use of both NT-proBNP and aortic diameter demonstrated better performance in predicting in-hospital mortality with sensitivity 79.3% and specificity 84.9% (Table 4) (Fig. 3).

Table 3
Multiple logistic regression for in-hospital mortality.

Clinical variables	OR	95% CI	P value
NT-proBNP ≥569.75 pg/ml	3.246	1.212–8.693	0.019
Aortic diameter ≥40 mm	2.917	1.102–7.722	0.031
Age ≥50 year	1.734	0.677–4.443	0.252
Type of AD	0.417	0.150–1.156	0.093
SBP ≥179 mmHg	1.595	0.067–4.193	0.344
TG ≥1.255 mmol/L	0.556	0.272–1.135	0.107

OR: odds ratio; CI: confidence interval.

4. Discussion

The present data showed the value of NT-proBNP in predicting in-hospital death in acute AD. Plasma NT-proBNP concentrations were significantly increased in patients who died with acute AD during hospitalization comparing to those who survived. Concentrations of NT-proBNP ≥569.75 pg/ml and aortic diameter ≥40 mm were important risk factors and independently associated with acute AD in-hospital mortality. Furthermore, NT-proBNP ≥1325.6 pg/ml or aortic diameter ≥47 mm demonstrated higher specificity in predicting in-hospital mortality. Using NT-proBNP and aortic diameter together showed better performance in predicting in-hospital mortality with higher sensitivity.

Ventricular volume expansion, overload vascular pressure, and inflammation had been reported to stimulate ventricular myocardium to release NT-proBNP [5,6,12]. NT-proBNP was a sensitive and specific indicator of left ventricular function. It demonstrated a variety of diagnostic and prognostic values for cardiovascular diseases [13]. Plasma NT-proBNP was reported in a series of studies to be an independent predictor of postoperative cardiac dysfunction, occurrence of atrial fibrillation, and other cardiovascular complications after cardiac surgery [14–17].

Hutfless et al. reported that plasma BNP > 385 pg/ml may predict the postoperative complications and one-year mortality after heart surgery [18]. Sbarouni et al. found elevated NT-proBNP levels in patients with acute AD and chronic aneurysm without complication compared to healthy normal subjects. The mechanism may be that many patients were accompanied by essential hypertension and ventricular diastolic dysfunction, which had close relationships with plasma BNP concentrations [19]. Moreover, Sodeck et al. demonstrated that NT-proBNP values could predict the outcome in patients with acute type A AD undergoing surgery. Elevated NT-proBNP levels especially beyond 647 pg/ml suggested poor prognosis [6].

Our findings illustrated the association of plasma NT-proBNP levels with short-term poor prognosis in patients with acute AD. Data showed that plasma NT-proBNP concentrations were significantly increased in patients who died compared to those who survived. NT-proBNP ≥569.75 pg/ml had close relationships with in-hospital mortality. Furthermore, NT-proBNP ≥1325.6 pg/ml showed higher specificity in predicting in-hospital mortality in acute AD.

NT-proBNP was considered to have the potential to inhibit vascular smooth cell proliferation and relax the normal rabbit aorta [20]. Plasma NT-proBNP levels had strong positive correlations with ascending and descending aortic diameter in healthy women with or without Turner syndrome. Furthermore, elevated NT-proBNP levels were associated with aortic aneurysm and/or dissection, and thus implicated into arterial wall homeostasis [21]. It was reported that SBP had positive, while DBP had negative correlations with plasma NT-proBNP levels [21,22]. Our data confirmed and extended these findings showing that aortic diameter, SBP were significantly higher in patients who died compared to those who survived. Moreover, aortic diameter had positive correlations with plasma NT-proBNP levels and admission DBP, respectively, which were partly inconsistence with previous studies. The exact mechanisms are not clear and need to be clarified.

Interestingly, in our pervious study, aortic diameter ≥48 mm was strongly associated with in-hospital mortality in acute type A AD [23]. While, in this present study, we systemically observed that aortic diameter ≥40 mm was an important risk factor and independently associated with acute AD in-hospital mortality. In the meanwhile, aortic

Table 4
Diagnostic value of NT-proBNP and aortic diameter for in-hospital mortality.

	AUC	Cut-off value	sensitivity	specificity	95% CI	P value
NT-proBNP (pg/ml)	0.799	1325.6	55.2%	95.7%	0.707–0.891	< 0.001
Aortic diameter (mm)	0.724	47	58.6%	88.2%	0.607–0.841	< 0.001
NT-proBNP + Aortic diameter	0.832	—	79.3%	84.9%	0.735–0.929	< 0.001

AUC: area under the curve; CI: confidence interval.

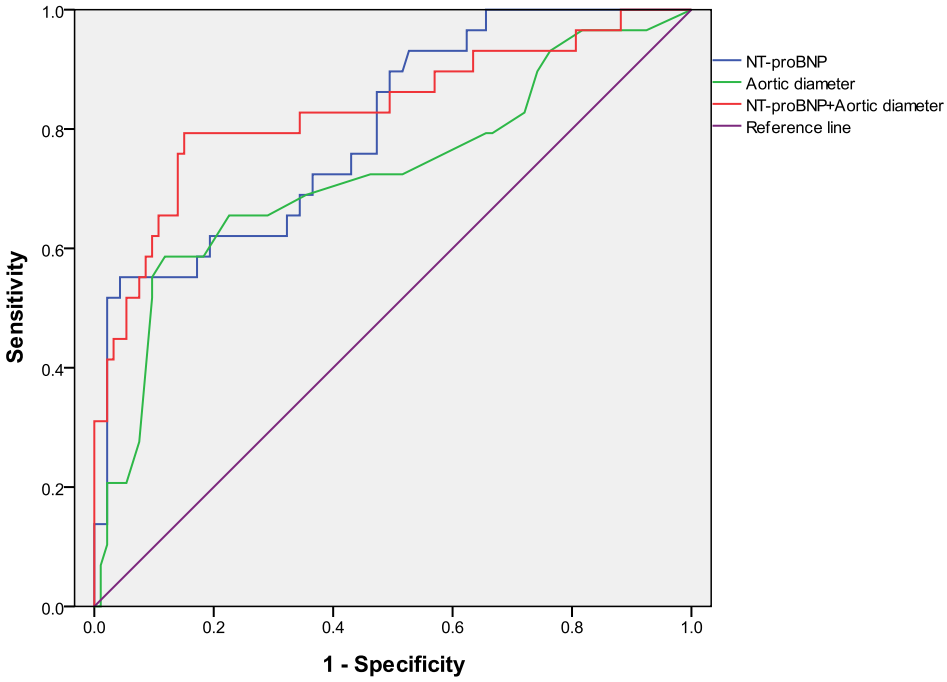

Fig. 3. Diagnostic value of NT-proBNP and aortic diameter for in-hospital mortality.

diameter ≥47 mm may predict in-hospital mortality with higher specificity in acute AD. In addition, although previous study had reported significant correlation between admission NT-proBNP levels and the time of onset of symptoms [6], our findings did not find such correlation. All the inconsistent findings might be due to the relative small sample size, which was the main limitation of this study. Therefore, larger, multicenter, and prospective cohort studies are needed to be performed to observe the potential role of NT-proBNP and aortic diameter in predicting in-hospital mortality in acute AD.

Furthermore, the data suggested that either plasma NT-proBNP levels or aortic diameter demonstrated important prognosis value in predicting in-hospital mortality with high specificity but relatively low sensitivity. When both NT-proBNP levels and aortic diameter were above the cutoff values mentioned above simultaneously, the sensitivity of mortality would be up to 79.3%, and thus, the risk of mortality may be increased. Therefore, observing both NT-proBNP levels and aortic diameter showed higher sensitivity in evaluating acute AD prognosis and may furtherly guide treatment in emergent clinical situations.

5. Conclusions

NT-proBNP ≥569.75 pg/ml and aortic diameter ≥40 mm were important risk factors and independently associated with acute AD in-hospital mortality. NT-proBNP ≥1325.6 pg/ml or aortic diameter ≥47 mm showed higher specificity in predicting in-hospital mortality. Using NT-proBNP and aortic diameter together showed better performance in predicting in-hospital mortality with higher sensitivity. However, further large and prospective clinical studies are still warranted to confirm these findings.

Conflict of interest

None.

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