Original Article

B-type natriuretic peptide in predicting the severity of community-acquired pneumonia

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BACKGROUND: Although pneumonia severity index (PSI) is widely used to evaluate the severity of community-acquired pneumonia (CAP), the calculation of PSI is very complicated. The present study aimed to evaluate the role of B-type natriuretic peptide (BNP) in predicting the severity of CAP.

METHODS: For 202 patients with CAP admitted to the emergency department, BNP levels, cardiac load indexes, inflammatory indexes including C-reactive protein (CRP), white blood cell count (WBC), and PSI were detected. The correlation between the indexes and PSI was investigated. BNP levels for survivor and non-survivor groups were compared, and a receiver operating characteristic (ROC) curve analysis was performed on the BNP levels versus PSI.

RESULTS: The BNP levels increased with CAP severity ($r=0.782$, $P<0.001$). The BNP levels of the high-risk group (PSI classes IV and V) were significantly higher than those of the low-risk group (PSI classes I–III) ($P<0.001$). The BNP levels were significantly higher in the non-survivor group than in the survivor group ($P<0.001$). In addition, there were positive correlations between BNP levels and PSI scores ($r=0.782$, $P<0.001$). The BNP level was highly accurate in predicting the severity of CAP (AUC=0.952). The optimal cut-off point of BNP level for distinguishing high-risk patients from low-risk ones was 125.0 pg/mL, with a sensitivity of 0.891 and a specificity of 0.946. Moreover, BNP level was accurate in predicting mortality (AUC=0.823). Its optimal cut-off point for predicting death was 299.0 pg/mL, with a sensitivity of 0.675 and a specificity of 0.816. Its negative predictive cut-off value was 0.926, and the positive predictive cut-off value was 0.426.

CONCLUSION: BNP level is positively correlated with the severity of CAP, and may be used as a biomarker for evaluating the severity of CAP.

KEY WORDS: Community-acquired pneumonia; B-type natriuretic peptide; Pneumonia severity index; Biomarker; Emergency; Disease severity assessment

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INTRODUCTION

Community-acquired pneumonia (CAP) is a leading infectious cause of death in developed countries.^[1,2] The timely and accurate evaluation of CAP severity is helpful to reduce the mortality, shorten hospital stay and save medical resources. It has been reported that pneumonia severity index (PSI) is closely associated with the mortality of patients, and has been widely used to evaluate the severity of CAP. However, the calculation of PSI is complicated and liable to personal errors. Researchers have found that the risk stratification of various infective

patients can be simplified by use of biomarkers.^[3–5]

B-type natriuretic peptide (BNP), also known as brain natriuretic peptide, is a 32-amino acid polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells (cardiomyocytes). BNP can cause natriuresis, the excretion of an excessively large amount of sodium in the urine. BNP has strong vasodilating and antihypertensive effect, and can antagonize the activity of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system. BNP plays an important role in regulating body fluid

volume, vascular pressure and electrolyte balance.^[6,7] Since natriuretic peptide levels are significantly increased in patients with severe sepsis and septic shock,^[8,9] the plasma concentration of natriuretic peptide can be used as a reliable indicator for identification of sepsis-induced myocardial inhibition.^[8] In recent years, the activation of proinflammatory cytokine and the sympathetic nervous system has also been identified as an inducing factor of BNP secretion.^[10,11] Accordingly, the severity of pneumonia can be reflected by BNP levels. In a pilot study, BNP level in selected patients with CAP can accurately predict the severity of the disease.^[12] A few studies have reported the use of BNP in emergency department patients with CAP. The purpose of this study was to evaluate the role of BNP in risk stratification of CAP based on clinical observations, laboratory measurements and chest X-ray examinations in the emergency department of a general hospital.

METHODS

Research subjects

Clinical data

A total of 202 patients with CAP were admitted to the emergency department (ED) of Fuxing Hospital from December 2011 to December 2012, including 96 males and 106 females, with age ranging from 18 to 96 years (81.67 ± 10.73 years).

Inclusion criteria

Eligible patients aged ≥ 18 years and presented with suspected CAP. Patients were evaluated in the ED by at least two physicians: a resident physician and a board-certified specialist of internal medicine.

Exclusion criteria

Patients with one or more of the following conditions were excluded: heart failure (according to case history, clinical manifestations, chest X-ray results and echocardiography evidences); coronary atherosclerotic heart disease; acute renal failure; end-stage renal disease; cirrhosis; hypertensive heart disease; pregnancy; pulmonary hypertension; pulmonary embolism; active tuberculosis; pulmonary fibrosis; nosocomial pneumonia; immunosuppressive diseases; primary aldosteronism; and hyperthyroidism.

Clinical grouping

Patients were divided into two groups based on PSI

classification: high-risk group (defined as PSI classes IV and V, 146 patients) and low-risk group (defined as PSI classes I–III, 56 patients). Moreover, patients were divided into two groups based on prognosis: survivor group (168 patients) and non-survivor group (34 patients).

Research methods

Laboratory and hemodynamic parameters were measured for patients upon enrollment to the emergency department, wherein the former included heart rate, systolic arterial pressure, diastolic pressure, body temperature and respiratory rate, and the latter included BNP, arterial blood gas, blood routine, liver function, kidney function, electrolytes, coagulation function and C-reactive protein (CRP). Within 24 hours after treatment, echocardiography (BNP > 100 pg/mL) and chest X-ray measurement were carried out in addition to conventional history inquiry, physical examination, and collection of relevant laboratory and imaging examination data. The severity of the disease was determined by PSI. Tracing collection of clinical information relevant to disease diagnosis and prognosis of patients was also performed.

CAP diagnostic criteria

CAP was defined by the presence of one or several of the following recently acquired respiratory signs or symptoms, including cough, sputum production, dyspnoea, core body temperature (> 38.0 °C), auscultatory findings of abnormal breath sounds and rales, white blood cell count ($> 10 \times 10^9$ or $< 4 \times 10^9$ cells/L) and an infiltrate on chest radiograph.^[13]

PSI classification criteria

Class I for patents aged < 50 years, without cancer, liver disease, cerebrovascular disease, kidney disease or other underlying diseases and abnormal vital signs; classes II–V were defined by calculation based on initial clinical assessment of age, underlying diseases, vital signs, epidemiological data, laboratory examination, blood gas analysis, radiological characteristics and other risk factors associated with pneumonia (class II: score less than 70; class III: score 71–90; class IV: score 91–130; and class V: score more than 130).

BNP concentration measurement

Collection of specimens included the following steps: 2 mL of peripheral venous blood was taken immediately

after enrollment of the patients; the specimens were put into a test tube containing ethylenediaminetetraacetic acid (EDTA) anticoagulant; and a quantitative point-of-care test of BNP concentration was performed.

BNP testing equipments and materials included the Triage Meter Plus as a dry rapid quantitative diagnostic apparatus for heart failure/myocardial infarction (diagnostic platform composed of access chemiluminescence, UniCelD×1800 intelligent large chemiluminescence immunoassay system and SynchronL×17125) and BNP antibody from US Biosite. Before the test, the BNP test panel stored at 2–8 °C was warmed to room temperature. 250 mL of EDTA anticoagulant blood sample was added into the wells of the test panel, which was incubated for 10–20 minutes. Subsequently, the panel was inserted into a Triage diagnostic apparatus for testing and the result was obtained after 15–30 minutes. BNP measurements ranged from 5.0 to 5 000.0 pg/mL.

Echocardiography

Echocardiography was performed using Hewlett-Packard SONO5500. Left ventricular ejection fraction (LVEF) and left ventricular end diastolic diameter (LVEDD) were calculated with the modified single-plane Simpson method. Echocardiography was performed by specialists who were unaware of the design of the study.

Statistical analysis

Data collation was performed by Excel 2010, and statistical analysis was made using SPSS 13.0 statistical software. Specifically, descriptive analysis of measurement data was performed using mean±standard deviation, whereas descriptive analysis of enumeration data was performed in the form of *n* (%). In addition, Student's *t* test was performed for the high- and low-risk groups. Linear correlation between BNP test values and PSI was analyzed. BNP data as the key values of severity stratification and death prediction and their sensitivity and specificity were determined by receiver operator characteristic (ROC) curves. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Patients

In the 202 patients aged 18–96 years with a mean age of (81.67±10.73), 96 were male and 106 were female. In 78% of the patients, cough, fever and dyspnea

were observed as major symptoms. According to PSI, 3 (1.5%) patients were grouped in class I, 8 (4.0%) patients in class II, 45 (22.2%) patients in class III, 89 (44.1%) patients in class IV, and 57 (28.2%) patients in class V.

BNP, CRP, WBC and PSI

BNP levels increased with the class of PSI (Table 1). BNP levels in the high-risk group were significantly increased compared with those in the low-risk group (*P*<0.01) (Table 2).

BNP levels increased with the severity of CAP (PSI classes) (Table 3). Similar results were obtained for CRP and WBC. We also found that the BNP levels of CAP patients with hypoxemia were significantly higher than those of patients without hypoxemia (263.8±151.0 pg/mL vs. 197.2±129.5 pg/mL, *P*=0.006).

CAP classification based on BNP was carried out using ROC curves, and BNP levels were highly accurate in predicting the low- and high-risk groups (Table 4, Figure 1).

Within 30 days after admission to the hospital, 34

Table 1. Comparison of BNP levels for PSI classes I–V

PSI class	Case number	BNP
I	3	21.6±17.5
II	8	45.7±37.7
III	45	79.4±55.6
IV	89	206.6±93.2 ^{*#Δ}
V	57	351.7±101.62 ^{*#Δ∇}

Comparison between class I and the marked class, ^{*}*P*<0.05; comparison between class II and the marked class, [#]*P*<0.05; comparison between class III and the marked class, ^Δ*P*<0.05; comparison between class IV and the marked class, [∇]*P*<0.05.

Table 2. Comparison of BNP levels between the low- and high-risk groups

PSI class	Case number	BNP	Statistics	<i>P</i>
I–III	56	71.5±54.3	11.537	0.000
IV–V	146	263.2±119.6		

Table 3. The results of correlation analysis between BNP levels and each of PSI classes, CRP levels and WBC

BNP	PSI score	CRP	WBC
Correlation coefficient (<i>r</i>)	0.782	0.560	0.513
<i>P</i>	0.000	0.000	0.000

Table 4. The sensitivity, specificity and accuracy of BNP levels in predicting the low- and high-risk groups

Variables	AUC area	Best cut-off points	Sensitivity	Specificity
BNP	0.952	125.000	0.891	0.946

patients (16.8% of 202 enrolled patients) died. The BNP levels in the non-survivor group upon admission to the hospital were significantly higher than those in the survivor group ($P<0.001$). Meanwhile, there was a significant difference in PSI scores ($P<0.001$) between the survivor group and the non-survivor group (Table 5).

Figure 1. ROC curve indicating the specificity and sensitivity corresponding to BNP levels in predicting the low- and high-risk groups.

Figure 2. ROC curves showing the specificity and sensitivity corresponding to BNP, PSI, CRP and WBC in predicting CAP mortality.

Various biomarkers for predicting CAP mortality evaluated by ROC curves are shown in Figure 2. Area under ROC curves (AUC) and likelihood ratios of different cut-off points are summarized in Table 6. BNP in predicting the mortality of CAP was more accurate than CRP and WBC, and it was similarly accurate as PSI.

DISCUSSION

BNP level positively correlated with the severity of CAP

In this study, the BNP level of the high-risk group (PSI classes IV and V) was significantly higher ($P<0.01$) than that of the low-risk group (PSI classes I-III). There was a significant positive correlation ($r=0.782$, $P<0.001$) between the level of BNP and PSI. Though the PSI has been accepted as a standard evaluation of pneumonia severity,^[14] the BNP level may indicate the severity of CAP. The results of the present study also showed that BNP is significantly superior to CRP and WBC in severity prediction. Therefore, the BNP level may be important for predicating the severity of CAP in clinical practice.

CAP severity classification using BNP values

The severity of CAP can be classified into five classes by PSI, but high-risk patients (hospitalization) and low-risk patients (no hospitalization) with CAP can be grouped by BNP level. When BNP was ≥ 125.0 pg/mL, the patients should be hospitalized immediately; when BNP level was <125.0 pg/mL, treatment may be given according to the specific situations of the patients at the outpatient clinic. As a biomarker for classification of CAP severity, BNP has a high specificity of 94.6% and a sensitivity of 89.1%, and it can provide important information for the evaluation and treatment of CAP.

Table 5. Difference analysis of variables between the survivor group and the non-survivor group

Variables	Survivor group	Non-survivor group	Student's <i>t</i> test	<i>P</i> value
BNP	183.0 $\pm$ 121.7	343.9 $\pm$ 125.5	-6.992	0.000
PSI score	106.6 $\pm$ 27.1	143.6 $\pm$ 25.7	-7.307	0.000

Table 6. The sensitivity, specificity and accuracy of various markers in predicting CAP mortality

Variables	AUC area	Best cut-off points	Sensitivity	Specificity	PPV	NPV	PLR	NLR
BNP	0.823	299.000	0.675	0.816	0.426	0.926	3.666	0.397
CRP	0.778	113.550	0.735	0.744	0.368	0.933	2.873	0.356
PSI	0.847	125.500	0.853	0.720	0.382	0.960	3.049	0.204
WBC	0.787	14.050	0.735	0.738	0.362	0.932	2.807	0.359

Positive predictive value (PPV)= $A/(A+B)$; negative predictive value (NPV)= $D/(C+D)$; positive likelihood ratio (PLR)=[$A/(A+C)$]/ $B/(B+D)$]; and negative likelihood ratio (NLR)=[$C/(A+C)$]/ $D/(B+D)$].

Death prediction using BNP values in patients with CAP

BNP can be used in accurately predicting death of CAP patients. In the present study, the prognosis accuracy of BNP was close to that of PSI (AUC 0.823 vs. 0.847), and was significantly better than that of common infection indicators such as CRP and WBC. When BNP was ≥ 299 pg/mL, the mortality (within 30 days) was significantly increased, whereas the majority of patients with BNP < 299 pg/mL survived, suggesting that when BNP level was ≥ 299 pg/mL, vital signs of patients should be closely monitored. If necessary, such patients should be admitted into the intensive care unit as soon as possible.

Advantages of BNP in prognosis of CAP

Recent studies have confirmed that B-type natriuretic peptide is a reliable indicator for the diagnosis of heart failure,^[15–16] and plays an important role in early diagnosis or differential diagnosis of acute dyspnea, especially cardiac dyspnea.^[17] In addition, the present study showed that the increased BNP level can accurately predict the death of CAP patients apart from those with heart failure, coronary heart disease or hypertensive heart disease. Furthermore, the level of BNP observed in the present study did not reach the levels commonly observed in patients with acute heart failure.^[16] Therefore, the increased BNP level of patients with CAP may be due to other causes. Some studies^[18–20] have suggested that BNP secretion is caused by tissue hypoxia which leads to pulmonary vasoconstriction, pulmonary hypertension and right ventricular overload. The patients with CAP usually suffer from localized hypoxia in the pulmonary circulatory system. In our study, there was a clear correlation between BNP level and blood oxygen saturation, suggesting that the above hypothesis may be one of the causes of the increased BNP level. A recent study^[11] found that inflammatory response can cause the release of BNP, and that BNP level and CRP value are significantly correlated. Other studies^[21,22] also found that IL-1b, IL-6, TNF- α and other proinflammatory cytokines can induce BNP secretion from cardiomyocytes cultured *in vitro*. Similarly, bacterial endotoxin was found to directly increase the expression of BNP mRNA in the myocardial cells of rat.^[23] Likewise, in our study, BNP was significantly correlated to CRP and WBC. Based on these findings, we hypothesized that with the severity of CAP, the increased BNP level was mainly caused by inflammatory response and local hypoxia in the pulmonary circulatory system, and that the level of BNP may reflect the severity of inflammatory

response as well as the degree of hypoxia.

PSI is widely used for accurate risk stratification of CAP through three-step calculation based on demographic data, complications, physical examination results, vital signs and experimental results. The patients can be divided into five groups according to the PSI scores.^[14] However, PSI has limitations in the emergency treatment. A recent study has shown that only 70% of 731 patients with CAP were classified by PSI.^[24] In contrast, rapid and simple BNP measurement can provide important information for clinicians in a very short time during emergency treatment about whether the patient needs hospitalization, whether the condition is life-threatening, etc.

In summary, the accurate evaluation of CAP severity, early identification of high-risk patients, and classification of treatment according to the severity can help to reduce mortality and improve the utilization of health care resources. By severity evaluation and prognosis with accuracy close to that of PSI, BNP can provide reliable data for timely, efficient and accurate classification of severity and for prognosis evaluation of CAP patients admitted to the emergency department.

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Ethical approval: The study protocol was approved by the Ethics Committee of Fuxing Hospital, Capital Medical University, Beijing, China.

Conflicts of interest: We have no conflicts of interest relevant to the study.

Contributors: All authors contributed to the design and interpretation of the study and writing of the manuscript.

REFERENCES

- 1 Niederman MS. Guidelines for the management of community-acquired pneumonia. Current recommendations and antibiotic selection issues. *Med Clin North Am* 2001; 85: 1493–1509.
- 2 Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch Intern Med* 2002; 162: 1059–1064.
- 3 Brueckmann M, Huhle G, Lang S, Haase KK, Bertsch T, Weiss C, et al. Prognostic value of plasma N-terminal pro-brain natriuretic peptide in patients with severe sepsis. *Circulation* 2005; 112: 527–534.
- 4 Morgenthaler NG, Struck J, Christ-Crain M, Bergmann A, Muller B. Pro-atrial natriuretic peptide is a prognostic marker in sepsis, similar to the APACHE II score: an observational study. *Crit Care* 2005; 9: R37–45.

- 5 Goto T, Takase H, Toriyama T, Sugiura T, Kurita Y, Tsuru N, et al. Increased circulating levels of natriuretic peptides predict future cardiac event in patients with chronic hemodialysis. *Nephron* 2002; 92: 610–615.
- 6 Langenickel T, Pagel I, Höhnelt K, Dietz R, Willenbrock R. Differential regulation of cardiac ANP and BNP mRNA in different stages of experimental heart failure. *Am J Physiol Heart Circ Physiol* 2000; 278: H1500–1506.
- 7 Cheung BM, Kumana CR. Natriuretic peptides-relevance in cardiac disease. *JAMA* 1998; 280: 1983–1984.
- 8 Post F, Weilemann LS, Messow CM, Sinning C, Münzel T. B-type natriuretic peptide as a marker for sepsis-induced myocardial depression in intensive care patients. *Crit Care Med* 2008; 36: 3030–3037.
- 9 Falcone M, Corrao S, Venditti M, Serra P, Licata G. Performance of PSI, CURB-65, and SCAP scores in predicting the outcome of patients with community-acquired and healthcare-associated pneumonia. *Intern Emerg Med* 2011; 6: 431–436.
- 10 Christ-Crain M, Breidhardt T, Stolz D, Zobrist K, Bingisser R, Miedinger D, et al. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. *J Intern Med* 2008; 264: 166–176.
- 11 Shor R, Rozenman Y, Bolshinsky A, Harpaz D, Tilis Y, Matas Z, et al. BNP in septic patients without systolic myocardial dysfunction. *Eur J Intern Med* 2006; 17: 536–540.
- 12 Mueller C, Laule-Kilian K, Scholer A, Perruchoud AP. B-type natriuretic peptide for risk stratification in community-acquired pneumonia. *J Intern Med* 2005; 258: 391–393.
- 13 Niederman MS. Guidelines for the management of community-acquired pneumonia. Current recommendations and antibiotic selection issues. *Med Clin North Am* 2001; 85: 1493–1509.
- 14 España PP, Capelastegui A, Quintana JM, Soto A, Gorordo I, García-Urbaneja M, et al. A prediction rule to identify low risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
- 15 McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *Am J Kidney Dis* 2003; 41: 571–579.
- 16 Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 2004; 350: 647–654.
- 17 Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D, et al. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. *Arch Intern Med* 2006; 166: 1081–1087.
- 18 Ando T, Ogawa K, Yamaki K, Hara M, Takagi K. Plasma concentrations of atrial, brain, and C-type natriuretic peptides and endothelin-1 in patients with chronic respiratory diseases. *Chest* 1996; 110: 462–468.
- 19 Hopkins WE, Chen Z, Fukagawa NK, Hall C, Knot HJ, Le-Winter MM. Increased atrial and brain natriuretic peptides in adults with cyanotic congenital heart disease: enhanced understanding of the relationship between hypoxia and natriuretic peptide secretion. *Circulation* 2004; 109: 2872–2877.
- 20 Yap LB, Mukerjee D, Timms PM, Ashrafian H, Coghlan JG. Natriuretic peptides, respiratory disease, and the right heart. *Chest* 2004; 126: 1330–1336.
- 21 Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J* 1999; 138: 285–290.
- 22 Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. *J Mol Cell Cardiol* 2004; 36: 505–513.
- 23 Tomaru Ki K, Arai M, Yokoyama T, Aihara Y, Sekiguchi Ki K, Tanaka T, et al. Transcriptional activation of the BNP gene by lipopolysaccharide is mediated through GATA elements in neonatal rat cardiac myocytes. *J Mol Cell Cardiol* 2002; 34: 649–659.
- 24 Ewig S, de Roux A, Bauer T, García E, Mensa J, Niederman M, et al. Validation of predictive rules and indices of severity for community acquired pneumonia. *Thorax* 2004; 59: 421–427.

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