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Original Article

Predictive role of NT-pro BNP for adverse cardiac events in community-acquired pneumonia: a retrospective study

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Abstract: Aims: We aim to investigate the predictive role of N-Terminal pro-B-type brain natriuretic peptide (NT-pro BNP) for adverse cardiac events in community-acquired pneumonia (CAP). Methods: A total of 372 consecutive patients with CAP in Beijing Luhe Hospital from January 2012 to December 2014 were included into this study. Based on initial serum CRP level, patients were separated into group A (<20 mg/L, group B (20-100 mg/L) and group C (>100 mg/L). Primary endpoint was the risk of major adverse cardiac events (MACE). Results: NT-pro BNP levels increased with CAP severity (r=0.58, P<0.001). Additionally, Plasma NT-pro BNP was correlated significantly with inflammatory markers. After a mean follow-up of 12.8 months, MACE occurred in 29 (7.8%) patients. There were no significant differences between the three groups in the length of ventilation, hospital length of stay and rate of cardiac mortality, heart failure and acute coronary syndrome. However, the risk of MACE was markedly different between the groups (P<0.05). NT-pro BNP levels of 210.5 ng/L was the boundary value of CAP-associated myocardial injury (sensitivity 84.2%, specificity 73.1%). Moreover, NT-pro BNP levels of 461.2 ng/L was the boundary value of MACE (sensitivity, 73.9%; specificity, 79.5%). Conclusions: Our study found that NT-pro BNP increased with severity of CAP increasing. Moreover, NT-pro BNP level was an effective predictor of cardiac injury and adverse cardiac events for patients with CAP, which might be related with bacterial endotoxins and inflammatory mediators. More studies are needed to confirm our finding.

Keywords: NT-pro BNP, community-acquired pneumonia, myocardial injury, major adverse cardiac events

Introduction

Community-acquired pneumonia (CAP) is caused by different etiology of acute infectious disease of the lungs [1]. The NICE clinical guidelines recommend using the C-reaction protein (CRP) level to guide antibiotic as follows: do not routinely offer antibiotic therapy if the CRP is less than 20 mg/L; consider a delayed antibiotic prescription if the CRP concentration is between 20 mg/L and 100 mg/L; and offer antibiotic therapy if the CRP concentration is greater than 100 mm/L [2]. CRP and pulmonary severity index (PSI) were used to assess the severity of community-acquired pneumonia and its short-term and long-term prognosis [3, 4]. Additionally, previous studies have shown that endotoxins can increase in BNP gene expression, causing BNP level increase [5]. N-Terminal pro-B-type brain natriuretic peptides (NT-pro BNP) have been used in predicting adverse cardiac events in patients with heart failure [6]. Moreover, many studies have shown the predictive potential of NT-pro BNP in patient with sepsis or septic shock. However, most studies were with short-term follow-up, and few studies evaluated the predictive value for adverse cardiac events in CAP patients. Therefore, our study was aimed to evaluate the predictive potential of NT-pro BNP for myocardial injury and adverse cardiac events in patients with CAP.

Materials and methods

Study population

We retrospectively analyzed the clinical data of 372 participants with CAP hospitalized in Beijing Luhe Hospital, Capital Medical University, from January 2012 to December 2014. Three patients were excluded owing to incomplete data. Our study was approved by the Bei-

Table 1. basic characteristics of patients in three groups

Variables	Group A (n=152)	Group B (n=126)	Group C (n=94)	F or χ^2 value	*P*
Sex (male, n)	58 (38%)	66 (52%)	57 (61%)	12.808	0.002
Age (year)	54.53±17.21	56.94±17.51	64.73±16.30*,#	10.66	0.000
COPD	4 (3%)	9 (7%)	2 (2%)	4.802	0.091
Asthma	7 (5%)	2 (2%)	1 (1%)	3.667	0.160
Hypertension	50 (33%)	46 (37%)	45 (48%)	5.693	0.058
CCI	12 (8%)	10 (8%)	15 (16%)	5.075	0.079
CAD	15 (10%)	18 (62%)	18 (19%)	4.282	0.18
DM	13 (9%)	25 (14%)	27 (29%)	17.129	0.000
AF	2 (1%)	1 (1%)	1 (1%)	0.70	0.704
T (°C)	36.57±0.547	37.11±0.94*	37.88±1.07*,#	70.17	0.000
HR (bpm)	78.38±3.41	82.54±13.52*	94.69±17.58*,#	37.08	0.000
R (rate/min)	19.32±1.35	19.76±1.80	20.85±.84*,#	17.79	0.000
SBP (mmHg)	128.68±17.28	126.48±15.93	129.53±19.81	0.94	0.393
DBP (mmHg)	79.86±10.70	76.10±9.42*	76.12±10.01*	6.21	0.002
PH	7.45±.041	7.47±0.035*	7.48±0.04*,#	24.94	0.000
PO_2 (mmHg)	89.87±19.01	82.68±18.24*	78.49±19.09*	11.64	0.000
PCO_2 (mmHg)	37.07±5.34	35.33±5.02*	33.74±7.10*,#	10.03	0.000
PO_2/FiO_2	403.39±73.55	356.98±85.88*	325.90±90.90*,#	27.40	0.000
cTNI (ug/L)	0.01 (0)	0.01 (0)	0.01 (0)*,#	15.85	0.000
NT-pro BNP (ng/L)	35 (62)	67 (201)*	427 (676)*,#	112.14	0.000
WBC ($\times10^9$/L)	6.74±2.45	8.51±3.74*	11.36±4.67*,#	48.89	0.000
NEUT ($\times10^9$/L)	4.22±2.20	6.39±4.43*	9.34±4.57*,#	54.94	0.000
ESR (mm/h)	20.88±17.17	40.45±21.96*	58.09±29.62*,#	74.94	0.000
CRP (mg/L)	7.16±6.01	55.68±24.01*	206.03±89.24*,#	532.19	0.000
PSI	51.97±20.25	57.94±23.25*	75.66±23.21*,#	34.31	0.000
PSI scale					
I	72 (47%)	50 (40%)	13 (14%)	29.206	0.000
II	51 (34%)	40 (32%)	26 (28%)	0.943	0.624
III	24 (16%)	25 (20%)	29 (31%)	8.097	0.017
IV	5 (3%)	11 (8%)	24 (25%)	30.755	0.000
V	0 (0%)	0 (0%)	2 (2%)	5.941	0.051

*Compared with group A; #Compared with group B. COPD, Chronic obstructive pulmonary disease; CCI, Chronic cerebral infarction; CAD, Coronary artery disease; DM, Diabetes mellitus; AF, Atrial fibrillation; PSI, Pulmonary severity index. *Data are mean ± standard deviation or n (%).*

jing Luhe Hospital Review Board. Inclusion criteria were (1) age≥18 year-old; (2) Temperature>37.3°C; (3) New cough, sputum, or existing symptoms of respiratory diseases, and purulent sputum, with or without chest pain; (4) WBC>10×10^9/L or WBC<4×10^9/L, with or without Nuclei move left; (5) Chest X ray shows patchy infiltrative shadows or interstitial changes, with or without effusion. Exclusion criteria were (1) tuberculosis, lung cancer, non-infectious interstitial lung diseases, pulmonary oedema, atelectasis, pulmonary embolism, pulmonary eosinophil infiltration and pulmonary Vasculitis; (2) congestive heart failure, (2) with liver or renal function failure; (3) acute coronary syndrome; (4) acute cerebrovascular events. Based on the initial CRP levels, patients were divided into three groups: Group A: CRP<20 mg/L; Group B: 20 mg/L≤CRP≤100 mg/L; Group C: CRP>100 mg/L.

Methods

We used the MINIVIDAS automatic biochemical analyzer to assess serum NT-pro BNP and cardiac troponin I (TNI). Additionally, NOVAPHOXPLUSL blood gas analyzer was used to detect PH, PO_2, PCO_2 and PO_2/FiO_2. The SYS-

Table 2. Outcomes of three groups in 12 months follow-up

Characteristic	Group A (n=152)	Group B (n=126)	Group C (n=94)	χ^2 value	*P* value
Hospital LOS (day)	12.1±8.1	14.9±11.6	17.4±15.3	2.64	0.16
Cardiac mortality	0 (0.0)	1 (0.8)	3 (3.2)	2.32	0.18
Heart failure	3 (2.0)	5 (4.0)	5 (5.3)	1.83	0.24
ACS	3 (2.0)	4 (3.2)	5 (5.3)	1.73	0.33
MACE (n/%)	6 (3.9)	10 (7.9)	13 (13.8)	4.51	0.03

MACE, Major adverse cardiovascular events; LOS, Length of stay; ACS, Acute coronary syndrome. Data are expressed as mean ± standard derivation or n (%).

Table 3. Risk factors of MACE

Variable	OR	95% CI	*P* value
Age	1.71	1.07-3.84	0.04
CRP	2.43	0.77-11.40	0.16
ESR	1.01	0.69-1.31	0.48
cTNI	1.83	0.80-7.29	0.13
NT-pro BNP	2.38	1.53-6.79	0.009
PSI	1.36	1.02-3.21	0.05

MACE, Major adverse cardiac events; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; TNI, Troponin I; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; PSI, Pneumonia severity index; OR, Odds ratios; CI, Confidence interval.

MEX (XT-1800I) was used to test the blood white blood cell (WBC). Serum C-reactive protein (CRP) level was tested by immune turbidimetry reagents with the HITACHI-7600. Pneumonia severity index (PSI) scoring system for patients with community-acquired pneumonia severity score PSI rating and can be used to assess the severity and prognosis of community-acquired pneumonia. We also recorded patients' clinical characteristics, such as temperature (°C), heart rate (HR, bpm), rate of breath, systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg).

All Patients were followed up for 12 months. We recorded clinical outcomes, including ventilation time, hospital length of stay, rate of cardiac mortality, heart failure and acute coronary syndrome (ACS). Additionally, the primary clinical outcome was major adverse cardiac events (MACE), which was the composite outcome of mortality, heart failure, and ACS.

Statistical analysis

All statistical analysis was performed with SPSS 21.0 (SPSS, Inc., Chicago, Ill). Continuous variables were expressed as mean ± SD or the median with interquartile range. Independent continuous variables were compared with 2-tailed Student t tests. Categorical variables were expressed as frequency or ratio and compared with the Pearson X^2 statistic. Additionally, the Spearman interclass correlation method was performed to evaluate the relationship between NT-pro BNP and other clinical variables. Stepwise multivariate logistic regressions were used to analyze the predictors of MACE. Receiver operating characteristic (ROC) curves were constructed, and the area under the ROC curve (AUC) was used to assess discriminant ability of the NT-pro BNP to predict the risk of MACE. The cutoff was the value that maximized the sensitivity and specificity. P<0.05 was statistically significant.

Result

Study population

There were 372 participants in our study, including 181 (48.6%) males and 191 females (51.4%). According to serum CRP level, all participants were separated into three groups: group A (CRP<20 mg/L), group B (20 mg/L≤ CRP≤100 mg/L) and group C (CRP>100 mg/L). The characteristics of two groups are illustrated in **Table 1**. There were no significant differences between two groups in rates of chronic obstructive pulmonary disease (COPD), asthma, hypertension, chronic cerebral infarction, coronary artery disease and atrial fibrillation. However, the three groups were statistically different in age, temperature, heart rate, DBP, PH, PCO_2, PO_2, PO_2/FiO_2, TNI, NT-pro BNP, WBC, ESR, CRP and PSI.

Outcomes

After a mean follow-up of 12.8 months, MACE occurred in 29 (7.8%) patients. The average length of ventilation was 11.9±8.1 hours, and average length in hospital was 15.5±12.8 d. There were no significant differences between the three groups in the hospital length of stay and rate of cardiac mortality, heart failure and ACS. However, the risk of MACE was markedly different between the groups (P<0.05). The outcomes are illustrated in **Table 2**.

Table 4. The correlation of NT-pro BNP and other clinical variables

NT-pro BNP	DBP	TNI	WBC	NEUT	ESR	CRP	PSI
rs	-0.05	0.26	0.28	0.36	0.35	0.57	0.58
P	0.344	0.000	0.000	0.000	0.000	0.000	0.000

NT-pro BNP, N-terminal pro-B-type natriuretic peptide; DBP, Diastolic blood pressure; WBC, White blood cell; NEUT, Neutrophil; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; PSI, Pneumonia severity index.

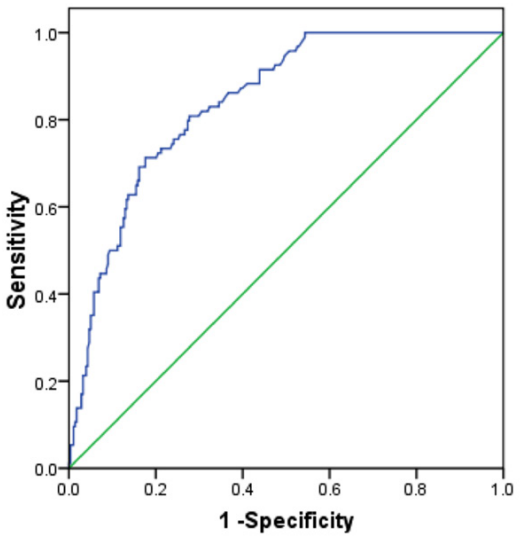

Figure 1. ROC curve of NT-pro BNP predicting infection related cardiac injury. ROC, receiver operating characteristic; NT-pro BNP, N-Terminal pro-B-type brain natriuretic peptides.

All factors possibly related to MACE were taken into logistic regression analysis (**Table 3**). Results showed that age (OR 1.71, 95% CI 1.07-3.84, P=0.04) and NT-pro BNP level (OR 2.38, 95% CI 1.53-6.79, P=0.009) were associated with the occurrence of MACE.

The correlation between NT-pro BNP level and other clinical variables was shown in **Table 4**. NT-pro BNP level was positively correlated with TNI (P<0.001), WBC (P<0.001), ESR (P<0.001), CRP (P<0.001) and PSI (P<0.001). However, the relationship between NT-pro BNP and TNI or WBC seemed weak (the Spearman's correlation coefficient<0.3). Additionally, there was no significant relationship between NT-pro BNPT and DBP (P=0.344).

The ROC curve of NT-pro BNP predicting pneumonia induced myocardial injury was illustrated in **Figure 1**. The AUC was 0.84 (OR 1.34; 95% CI 1.13-1.49, P<0.001). NT-pro BNP level of 210.5 ng/L was the boundary value of pneumonia induced myocardial injury (sensitivity 84.2%, specificity 73.1%). Additionally, the AUC of NT-pro BNP predicting MACE was 0.73 (OR 1.29, 95% CI 1.11-1.38, P<0.001). NT-pro BNP levels of 461.2 ng/L was the boundary value of MACE (sensitivity, 73.9%; specificity, 79.5%) (**Figure 2**).

Discussion

In consistent with previous studies, our study demonstrated that NT-pro BNP levels increased with CAP severity. Moreover, NT-pro BNP was significantly related to major cardiac events and, a NT-pro BNP level of 210.5 ng/L was the boundary value of infection induced cardiac injury. Additionally, NT-pro BNP level of 461.2 ng/L identifies patients with risk of MACE. More studies are needed to confirm our findings.

In patients with CAP, NT-pro BNP levels are powerful predictors of adverse cardiac events. Many studies have proved that NT-pro BNP could be used for the detection, stratification, and prognosis in patients with heart failure and coronary artery disease. For patients with systemic inflammatory response syndrome (SIRS), Chen et al found that compared with non-SIRS patients, subjects with SIRS had a markedly higher level of brain natriuretic peptide (BNP). Additionally, BNP level of more than 113 pg/mL was independent predictor of all-cause mortality in septic patients [7]. However, in patient with pneumonia, Krüger S et al found that mid-regional pro-atrial natriuretic peptide (MR-proANP) was an independent predictor of 28-days mortality (AUC 0.80, 95% CI 0.76-0.84) in the CAPNETZ database [8]. Although CRP is regarded a sensitive biomarker of infection, it predictive role for the outcome is not definitely affirmed. Cheng et al found that the NT-pro BNP level at 4542 ng/mL predicted mortality with a sensitivity of 68.8% and a specificity of 69.5%. Furthermore, they found that NT-pro BNP was superior to CRP in predicting mortality and, the predicting mortality of APACHE II score or CRP was improved only when combined with both NT-pro BNP and TNI [9]. Additionally, in 302 CAP patients, Christ-Crain et al confirmed that BNP levels increased with rising disease severity as classified by the PSI (P=0.01). Moreover, ROC analysis for the prediction of survival

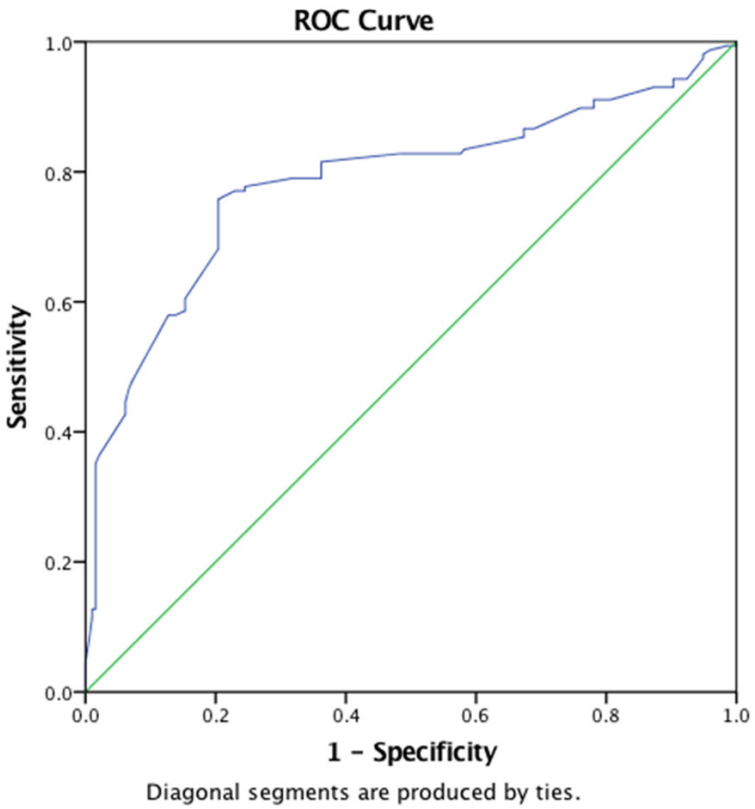

Figure 2. ROC curve of NT-pro BNP predicting MACE. ROC, receiver operating characteristic; NT-pro BNP, N-Terminal pro-B-type brain natriuretic peptides; MACE, major adverse cardiac events.

showed that the AUC for BNP was comparable to the AUC of the PSI (0.75 vs. 0.71, P=0.52) [10]. Li et al confirmed that BNP could be used as a biomarker for evaluating the severity of CAP. They recommended BNP level of 299.0 pg/mL in predicting in-hospital mortality (sensitivity 67.5%, specificity 81.6%) [11]. In consistent with previous studies, our study confirmed that NT-pro BNP increased with the severity of pneumonia. Moreover, NT-pro BNP level of 210.5 ng/L predicting inflammation induced cardiac injury and level of 461.2 ng/L predicting CAD patients with risk of adverse cardiac events. However, more studies are needed to confirm our findings.

Compared with BNP and MR-pro ANP, NT-pro BNP was the best predictor of long-term risk of mortality. BNP is the most extensively used for CAP patients' risk stratification. The MR-pro ANP has the advantages of preanalytic stability and more suitable for primary care and laboratory transfers. NT-pro BNP is a more promising predictor as its levels seem to be more dependent on kidney function, therefore, better reflecting cardio-renal interactions than other natriuretic peptides. Previous studies have demonstrated that MR-pro ANP carried a comparable diagnostic accuracy as BNP and NT-pro BNP in patients with heart failure [12]. In CAP patients, the predictive potential of NT-pro BNP seems to be superior to other natriuretic peptides. Nowak et al found that the predictive potential in short-term mortality of three natriuretic peptides was comparable (NT-pro BNP vs MR-proAN P=0.86, NT-pro BNP vs BNP P=0.10, MR-pro ANP vs BNP P=0.25) [13]. However, the predictive potential of NT-pro BNP in long-term mortality was significantly better than that of BNP (P=0.02) whereas MR-pro ANP achieved comparable accuracy as NT-pro BNP (P= 0.22). Importantly, the predictive value of all natriuretic peptides was comparable to that of PSI. Nowak et al confirmed that the all natriuretic peptide showed similar potential in predicting short- and long-term mortality [13]. Furthermore, NT-pro BNP helped to separate "PSI high" patients into a medium- and high-risk group. PSI is widely used and validated tool. It used a three-step algorithm including demographics, comorbidities, physical examination, vital signs and various laboratory findings. The calculation is bothersome and partially dependent on individual impressions. Therefore, natriuretic peptides, especially NT-pro BNP, are simple and powerful alternative predictors for short- and long-term mortality for patients with CAP.

The mechanism for cardiac dysfunction and cardiac injury in patients with pneumonia might be related to inflammatory stimuli and myocardial inhibition. Up to now, NT-pro BNP level increased in patients with ventricular systolic dysfunction, which was related with atrial and ventricular stretch. However, heart failure is also a state of hyperinflammation. In the SOLVD

trial, Torre-Amione et al found that circulating levels of proinflammatory cytokines (TNF-α, IL-6) increased in patients as their cardiac function deteriorated [14]. Proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) are associated with the severity of left ventricular dysfunction and correlate with the degree of activity of the renin angiotensin and sympathetic system. More importantly, inflammatory markers (TNF-α, IL-1β, IL-6) have proven capable of increasing the ability of cultured myocytes in vitro to secrete NT-pro BNP. Additionally, these inflammatory markers could also damage cardiac muscles directly. Concordantly, bacterial endotoxin was also found to directly increase the expression of BNP mRNA in rat myocytes [15]. BNP was a marker for sepsis-induced myocardial depression in ICU. Shor et al found that serum BNP is positively correlated with CRP levels in septic patients without clinical or echocardiographic evidence of systolic dysfunction [16]. Meader et al have demonstrated BNP levels above 500 pg/mL in patients with sepsis and normal left ventricular function [17]. Thus NT-pro BNP levels appear to reflect the extent of systemic inflammation in pneumonia. In consistent with these studies, our study also confirmed that NT-pro BNP increased with the severity of pneumonia. NT-pro BNP level was positively correlated with inflammatory markers such as WBC, ESR, CRP and PSI. Therefore, the cardiac dysfunction in CAP might be related with inflammatory mediators. However, more studies are needed to explore the exact mechanisms.

Limitations

There are several limitations in this study. First, this is a retrospective study, and more high quality studies are needed to confirm our findings. Second, the sample size of participants was relatively small, which will likely have reduced the statistical power for data analysis. Third, all patients enrolled in our study were followed by 12.8 months, and more long-term follow-up data are needed to explore the predictive role between NT-pro BNP and clinical outcome. Therefore, large studies with longer follow-up and careful matching of key clinical variables are needed.

Conclusions

In our study, the high NT-pro BNP level was an independent predictor for the 1-year rate of MACE in CAP patients, which was positively correlated to disease severity and inflammatory markers, such as CRP, ESR and PSI. However, whether plasma NT-pro BNP level is a prognostic factor for CAP needed to be confirmed in more studies.

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Disclosure of conflict of interest

None.

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