Serum N-terminal pro-brain natriuretic peptide level is a significant prognostic factor in patients with severe sepsis among Southwest Chinese Population

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Abstract. – BACKGROUND: This study aimed to determine the predictive value of elevated N-terminal pro-brain natriuretic peptide (NTproBNP) for mortality in patients with severe sepsis.

PATIENTS AND METHODS: This was a retrospective study in Emergency Department of Sichuan Provincial People's Hospital, and patients were screened between January 1, 2009 and December 31, 2011. Demographic and clinical data as well as Acute Physiology And Chronic Health Evaluation II (APACHE II) and Sepsis Organ Failure Assessment (SOFA) scores were collected within the first day of admission. Survival was determined to establish its association with the NT-proBNP using logistic regression and receiver operating characteristic (ROC) curve.

RESULTS: A total of 171 patients with severe sepsis were analyzed. The median APACHE II and SOFA scores were 11 (IQR, 7-16) and 3 (IQR, 1-5), respectively. The median C-reactive protein (CRP), procalcitonin (PCT) and NT-proBNP was 10.3 mg/dL (IQR, 3.4-21.4 mg/dL), 0.4 ng/mL (IQR, 0.2-3.6 ng/mL), and 954 (321-1576) pg/mL, respectively. The median NT-proBNP in survivors was 584 pg/mL (IQR, 321-875 pg/mL) versus 1271 (IQR, 851-1576 pg/mL) in nonsurvivors (p < 0.001). In the ROC curves, the area value was 0.89 for serum NT-proBNP, and its potent cutoff value was 1500 pg/mL. After multivariate regression analysis, NT-proBNP was significantly correlated with the mortality of severe sepsis (OR = 1.58, 95% CI 1.36-1.77).

CONCLUSIONS: Serum NT-proBNP is frequently increased in severe sepsis patients, and non-survivors have higher levels than survivors. High levels of admission NT-proBNP are associated with mortality.

Key Words:
 N-terminal pro-brain natriuretic peptide, Severe sepsis, Prognostic factor.

Introduction

Sepsis is a clinical syndrome, and it has become the most common cause of mortality in the intensive care unit (ICU) despite improvements in antimicrobial therapy and supportive care, with a high mortality ranging from 28% to 50%[1,2]. Early identification of patients at high risk of death after admission may help determine therapeutic interventions, such as changes in therapeutic protocols or further diagnostic procedures aiming at preventing shock and multiple organ failure with all their sequels that could have an important impact on reducing patients' mortality[3-5]. Thus, it is necessary to identify patients at high risk of death, either through readily available laboratory tests or clinical criteria. In past decades, lots of studies tried to establish prediction models or scoring systems to determine the clinical outcomes of sepsis, and Acute Physiology And Chronic Health Evaluation II (APACHE II), Sepsis Organ Failure Assessment (SOFA), and Simplified Acute Physiology Score (SAPS) have been developed and used to identify patients with increased risk of death and organ dysfunction[6-9]. However, all those prediction models or scoring systems were of relative complexity, and lack "novel" blood markers for the diagnosis and specific monitoring of patients with sepsis.

It has been reported that sepsis is commonly associated with congestive heart failure (CHF)[10,11], and CHF strongly affects the prognosis of patients with sepsis. In the last few years, interest has focused on the clinical utility of brain natriuretic peptide (BNP) in the setting of Intensive Care Unit (ICU). Recently, both BNP

and N-terminal pro-brain natriuretic peptide (NTproBNP) had been shown to be strongly associated with risk of acute CHF, and both of them had become to be a simple, inexpensive, commonly available test that reflects closely the activation of the coagulation system and the severity of the host response[12,13]. Recently, more and more studies reported that serum elevated BNP or NTproBNP was common in patients with sepsis[14]. However, it is still unknown whether elevated BNP or NTproBNP was correlated with the occurrence, development and clinical outcomes of sepsis.

Previous studies showed that NT-proBNP concentrations were very stable in blood and circulating levels were higher than those of BNP. In present study, we therefore aimed to observe the dynamic changes of NT-proBNP in a cohort of stable patients with sepsis, so as to determine whether serum NT-proBNP could be used as an early marker in predicting mortality of patients with sepsis.

Patients and Methods

Study Design and Patients

This was an observational, retrospective study of patients with sepsis admitted to the Emergency Department of Sichuan Provincial People's Hospital from January 2008 to December 2011. The following data were recorded: age, sex, reason for admission, C-reactive protein (CRP) procalcitonin (PCT), NT-proBNP, disease severity according to the APACHE II score and degree of organ dysdunction quantified by SOFA score. The local Ethics Committee of our Hospital approved the collection of samples for the analysis of above biomarkers after receiving oral informed consent.

In present study, the diagnosis of sepsis is based on the 1992 American College of Chest Physicians consensus criteria[15], which requires the presence of proven infection and two or more features of Systemic Inflammatory Response Syndrome (SIRS): (1) Fever or Hypothermia (temperature over 38 or under 36 degrees Celsius); (2) Tachypnea (Respiratory rate over 20); (3) Tachycardia (Heart Rate over 90); (4) Immune Dysregulation (White Blood Cell count less than 4000, greater than 12,000, or greater than 10% immature forms). Patients were excluded if they had chronic heart insufficiency or preexistent renal insufficiency.

Laboratory Measurements

Serum biochemistry was analyzed with a standard multi-channel biochemical analyzer, and NTproBNP was measured by immunoassay (Elecsys, Roche Diagnostics, Mannheim, Germany). Serum PCT concentrations were measured by immunoluminometric assay (VIDAS BRAHMS PCT, BioMerieux, Marcy l'Etoile, France) with a detection limit of 0.05 ng/mL. Serum CRP was measured by an immunoturbidimetric assay using an ARCHITECT c-System (Abbott Laboratories, Abbott Park, IL, USA) with a detection limit of 0.5 mg/dL.

Statistically Analysis

Data entry and statistical comparisons were made with the statistical package SPSS version 9.0, (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as medians with interquartile range (IQR) or as means with SDs, according to their distributions, and categorical variables are presented with absolute and relative frequencies. The *t*-test or Mann-Whitney U test was used for quantitative data comparison, and chi square test was used for categorical data comparison. A two-tailed *p* value of < 0.05 was considered to be statistically significant. To explore the prognostic value of the NTproBNP in mortality, we performed receiver operating characteristic (ROC) curve and calculated its area under the curve (AUC), and the optimal cutoff value was chosen based on a maximum sum of sensitivity and specificity. Additionally, logistic regression method was used including other interested variables to further verify the value of serum NT-proBNP in predicting the outcomes of patients with severe sepsis.

Results

General Information

A total of 171 severe sepsis patients with a mean age of 54.6 years were analyzed in this study, consisting of 101 male and 70 female. Among those patients, 78 patients (45.6%) had no comorbidity. In those 93 patients with comorbidity, 37.6% (35/93) patients had diabetes mellitus, 25.8% (24/93) had chronic obstructive pulmonary diseases, and 23.7% (22/93) had hypertension. The median score of APACHE II and SOFA on admission was 11 (IQR: interquartile range 7-16) and 3 (IQR, 1-5), respectively. And the median level of CRP, PCT and NT-proBNP

was 10.3 mg/mL (IQR, 3.4-21.4), 0.39 ng/mL (IQR, 0.2-3.6), and 954 pg/mL (321-1576), respectively. In this cohort, a total of 67 patients died and 104 patients survived, and the overall mortality rate was 43.2%.

The Characteristics According to the Survival of Patients

The main clinical and laboratory characteristics according to the survival of severe sepsis were also presented in Table II. As compared to survivors, nonsurvivors were in a more severe condition as reflected by the higher APACHE II and SOFA scores, and had higher creatinine levels on admission. In survivors, the median level of CRP, PCT and NT-proBNP was 9.6 mg/mL (IQR, 3.3-16.5), 0.25 ng/mL (IQR, 0.2-2.7), and 584 pg/mL (321-875), respectively; while in non-survivors, the median level of CRP, PCT and NT-proBNP was 15.6 mg/mL (IQR, 8.2-21.4), 0.47 ng/mL (IQR, 0.3-3.5), and 1271 pg/mL (851-1576), respectively; and the difference in either CRP, PCT or NT-proBNP between survivors and nonsurvivors was statistically significant, respectively.

Prognostic Value of Serum Variables and Severity Scores

The discriminatory ability for mortality was determined by the ROC curve analysis for each biomarker and for severity scores. The area under the ROC curve with regard to mortality prediction was 0.71 for CRP, 0.76 for PCT, 0.89 for NT-proBNP, 0.84 for APACHE II score and 0.75 for SOFA score. The differences between the areas under the ROC curve of NT-proBNP vs APACHE II and SOFA scores were statistically significant. The cutoff in NT-proBNP that best

Table I. Clinical and laboratory characteristics on admission.

	Variables
Age, y	54.6 ± 9.8
Male gender, n (%)	101 (59.1)
APACHE II score	11 (7-16)
SOFA score	3 (1-5)
Comorbidities, n (%)	93
Diabetes mellitus	35 (37.6)
COPD	24 (25.8)
Hypertension	22 (23.7)
Creatinine, mg/dL	1.2 (0.7-1.6)
CRP, mg/mL	10.3 (3.4-21.4)
PCT, ng/mL	0.4 (0.2-3.6)
NTproBNP, pg/mL	954 (321-1576)

predicted mortality was 1500 pg/mL, having a sensitivity of 89%, a specificity of 87%, a positive predictive value of 86%, and a negative predictive value of 90%.

Multiple logistic regression analysis revealed that APACHE II score (OR1.04, 95%CI 1.01-1.43) and NT-proBNP (OR: Odds ratio: 1.58, 95%CI 1.36-1.77) were significantly and independent outcome predictors. In contrast, sex, age, comorbidities, creatine, CRP, PCT and SOFA score were not associated mortality.

Discussion

The mortality of sepsis remains high despite advancements in supportive care, and much effect has been used to identify factors that confer useful information regarding severity and outcome. Recently, the use of BNP as prognostic indicators in critical illness has aroused some interest[16-18]. As reported, BNP is produced as a

Table II. Clinical and laboratory characteristics according to the survival of patients.

Variables	Survivors (N = 104)	Non-survivors (N = 67)	p value
Age, y	50.1 ± 7.6	56.6 ± 9.4	< 0.001
Male gender, n (%)	63 (60.6)	38 (56.7)	0.616
APACHE II score	9 (5-13)	13 (9-17)	0.007
SOFA score	2 (1-4)	4 (3-6)	0.011
Comorbidities, n (%)			
Diabetes mellitus	14 (40.0)	21 (45.7)	0.445
COPD	9 (25.7)	15 (32.6)	
Hypertension	12 (34.3)	10 (21.7)	
Creatinine, mg/dL	0.8 (0.6-1.3)	1.4 (0.9-1.7)	0.032
CRP, mg/mL	9.6 (3.3-16.5)	15.6 (8.2-21.4)	0.004
PCT, ng/mL	0.25 (0.2-2.7)	0.47 (0.3-3.5)	0.021
NTproBNP, pg/mL	584 (321-875)	1271 (851-1576)	< 0.001

prohormone, which is cleaved into the active BNP and the inactive NT-proBNP molecule; the former reflecting rapid changes and the latter less acute alterations[12]. And both peptides are reliably measured, and their concentrations are affected by the same variables and have comparable diagnostic and prognostic accuracy. In present study, we found that high serum NT-proBNP levels were associated with mortality, and serum NT-proBNP levels above 1500 pg/mL serve as a strong independent indicator of mortality in this cohort. Indeed, this finding was consistent with previous investigations, which also suggested that elevated BNP or NT-proBNP levels may prove to be powerful predictors of mortality in patients with sepsis[19,20]. In patients with sepsis, the serum elevation of NT-proBNP may be related to sepsis-related cardiac dysfunction and inflammatory response. However, its exact mechanism in sepsis was not fully understood at present.

Currently, the biological effects of BNP was well documented in patients with ventricular dysfunction, which include dieresis, natriuresis, vasodilation, and inhibition of the activities of several networks such as the renin-angiotensin-aldosterone system, cytokines, and the sympathetic nervous system. However, those effects of BNP in sepsis would exacerbate disease progression in theory, as it would result to a further decline in circulating volume. So, for patients with sepsis, some scholars inferred that NT-proBNP was not only a molecular marker for the predicting of severity of the disease, but also a promoter for disease progression.

To date, several biomarkers have been identified to have some prognostic value in the field of sepsis. For example, both elevated PCT and cardiac troponin were reported to be associated with higher mortality in septic patients[21,22]. In present study, the sensitivity and specificity of elevated BNPs for predicting mortality in septic patients were 87% and 84%, respectively, and they were higher to that of elevated PCT and other biomarkers. Thus, NT-proBNP would be a potential biomarker to predict which patients were at greater risk of dying due to sepsis. However, due to the role of BNP in the systemic inflammatory response is not yet clear, and physiological and pathological significance of NT-proBNP in sepsis patient needs further study, we hypothesized that a combination of NT-proBNP measurement with other biomarkers or scoring system (such as APACHE II) would be more reasonable.

This study is a single-center retrospective study, and the sample size is relative small, which maybe affect the representativeness of the sample to some extent. Moreover, some other confounding factors (such as volume load, uniformity of treatment programs, et al) still exist, which may influence the prognosis of patients. To overcome these issues, a well-designed multi-center trial with more patients is mandatory to validate our findings. However, our data still shed new light on the clinical significance of NT-proBNP in predicting of mortality.

Conclusions

In patients with sepsis, elevated NT-proBNP is associated with disease severity and increased mortality. In particular, patients with admission NT-proBNP more than 1500 pg/mL were at high risk of dying than patients with lower levels.

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