Original Contribution

Prognostic significance of brain natriuretic peptide obtained in the ED in patients with SIRS or sepsis

Yunxia Chen MM\textsuperscript{a,1}, Chunsheng Li MD\textsuperscript{b,*}

\textsuperscript{a}Emergency Department of China Rehabilitation Research Center, Beijing 100068, China
\textsuperscript{b}Emergency Department, Beijing Chaoyang Hospital of the Capital Medical University, Beijing 100020, China

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Abstract

Purpose: The study was conducted to know the significance of brain natriuretic peptide (BNP) for prognosis of septic patients.

Methods: The subjects were 1000 patients selected in emergency department of Beijing Chaoyang Hospital of the Capital Medical University (Beijing, China) and were classified into 3 groups as follows: systemic inflammatory response syndrome (SIRS), non-SIRS, and sepsis groups. Plasma serum brain natriuretic peptide (BNP) levels and the positive detection rates of BNP were examined. The BNP level of 100 pg/mL or more was regarded as positive, and then the positive detection rates of BNP of these groups were compared. The prognostic values of BNP and APACHE (Acute physiology and chronic health evaluation) II score for the 28-day mortality were investigated, and their cutoff values for death were determined.

Results: There were significant differences in the positive detection rates of BNP between any 2 groups and in 28-day mortality between the patients with SIRS and non-SIRS groups. The BNP level had positive correlation to APACHE II score in 3 groups. Brain natriuretic peptide level of more than 113 pg/mL was independent predictor of death in septic patients.

Conclusion: The positive rates of BNP in SIRS and septic patients were significantly higher than that of non-SIRS patients, and this is an index for unfavorable prognosis in septic patients.

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1. Introduction

The brain natriuretic peptide (BNP) level is a marker for the clinical evaluation of cardiac functions. It has been used for the detection, stratification, and prognosis of congestive heart failure\cite{1-2}. Previous investigations have reported that the BNP level in the patients with sepsis, severe sepsis, and septic shock correlates with their prognosis\cite{3-4}. However, the sample sizes of most of these investigations were relatively small, the inclusion criteria were different, and the conclusions cannot be generalized. We discussed the significance of BNP level for the prognosis of the patients by comparing the positive detection rates of the patients who had systemic inflammatory response syndrome (SIRS), non-SIRS, and sepsis in emergency department.
2. Subjects and methods

2.1. Subjects and grouping

The selected subjects were 640 patients with SIRS remedied from December 2006 to September 2007. All of the included subjects satisfied the criteria for SIRS diagnosis that were formulated on the International Meeting of Sepsis Definition in Washington in 2001 [5]. Among selected patients, 368 were male and 272 were female, aged between 19 and 96 years old (mean, 68.3 ± 14.1). There were 327 patients in the sepsis group, including 198 male and 129 female cases, aged between 21 and 96 years old (mean, 69.5 ± 13.4). There were 313 cases in the SIRS group, including 170 male and 143 female cases, aged between 19 and 94 years old (mean, 67.1 ± 14.8). Meanwhile, the control group included 360 patients remedied in the rescuing wards, including 213 males and 147 females, aged between 22 and 91 years old (mean, 67.3 ± 12.5). They did not satisfy the criteria for SIRS but needed treatment and monitor immediately including patients with coma, shock, toxicosis, acute abdomen, stroke, trauma, and others.

2.2. Data collection

The data including age, sex, previous medical record, and vital signs were immediately carried out when patients were included. Examinations such as blood routine examination, blood gas, biochemical examinations, and APACHE II score were carried out within 24 hours.

2.3. Measurement method for BNP

To measure the level of BNP, 2 mL of ulnar venous blood was collected from each patient and then added into the test tubes containing edetate sodium for rapid detection of BNP at bedside. Triage BNP detector (Triage BNP, Biosite Company, San Diego, Calif; there are no conflicts of interest) was used for the detection for 15 minutes. The detection range of Triage BNP detector was 5 to 5000 pg/mL, and the values less than 5 pg/mL were displayed and recorded as 5 pg/mL, whereas BNP level of 100 pg/mL or more in the plasma was treated as the positive standard [6].

2.4. Statistical analysis

All of the data were dealt with SPSS 11.5 software (SPSS Inc, Chicago, Ill). Plasma BNP level and APACHE II score were data with nonnormal distribution and expressed as median (25%-75% quartile). The data with normal distribution were expressed as \(\bar{x} \pm SD\). The \(\chi^2\) test was used to compare the positive rate and mortality, and \(P < .05\) was considered to be statistically significant. Logistic regression analysis was used to determine the independent predictors for death, and receiver operating characteristic curve was used to determine the cutoff value for the predictor of death. Spearman interclass correlation method was used to analyze the correlation between BNP and APACHE II score.

2.5. End point of the study

For those patients, 28-day follow-up was performed, and the survival or death of the patients within 28 days was considered as the end point and were documented.

3. Results

3.1. Comparisons in the basic conditions for the included cases

No statistical difference in age and sex was found in these groups \((P > .05)\). Many cases of heart diseases and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparisons in the basic conditions of non-SIRS group, SIRS group, and sepsis group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-SIRS group</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>67.3 ± 12.5</td>
</tr>
<tr>
<td>Male (%)</td>
<td>59.3</td>
</tr>
<tr>
<td>Basic diseases</td>
<td></td>
</tr>
<tr>
<td>Heart disease (%)</td>
<td>31.7</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>46.4</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>14.2</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>9</td>
</tr>
<tr>
<td>Asthma (%)</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>1</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>8</td>
</tr>
<tr>
<td>Others (%)</td>
<td>7.5</td>
</tr>
<tr>
<td>No basic disease (%)</td>
<td>12.5</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>9 (6-14)</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>64 (24-228)</td>
</tr>
<tr>
<td>28-day mortality (%)</td>
<td>17.8</td>
</tr>
</tbody>
</table>

COPD indicates chronic obstructive pulmonary disease; APACHE, acute physiology and chronic health evaluation.
hypertension were found in non-SIRS group in comparison to those in sepsis group and SIRS group \((P < .05)\), whereas relatively, there are more cases of chronic obstructive pulmonary disease and cerebrovascular diseases accompanied with sepsis as basic diseases \((P < .05)\), which may be related to the liable recurrence of these diseases. The 28-day mortality and APACHE II score in sepsis group and SIRS group were higher than that in non-SIRS group \((P < .05)\), indicating that the complication of SIRS or sepsis will aggravate the patient’s conditions and increase the 28-day mortality (Table 1).

### 3.2. Comparison in the positive detection rate of BNP in septic, SIRS, and non-SIRS patients

The positive detection rate of BNP in the cases from the 3 groups and the comparison results were shown (Table 2), with the highest positive detection rate in the SIRS group \((P < .01)\), the lowest in the non-SIRS group \((P < .001)\), and the middle in sepsis group. The positive detection rates of BNP were higher in SIRS and sepsis group \((P < .001)\). The BNP concentration increased after the concurrent of infection, confirming that infections or inflammatory factors may induce the increase in BNP concentration, and it was not merely induced by myocardial dysfunction.

### 3.3. Comparison of the 28-day mortality when BNP was positive

The 28-day mortality in these groups was compared when BNP was positive (Fig. 1), in which the highest 28-day mortality was in sepsis group \((P < .01)\), lowest in non-SIRS group \((P < .01)\), and middle in SIRS group, with no significant difference between sepsis group and SIRS group \((P > .05)\).

### 3.4. Comparison of the usefulness of BNP and APACHE II score as a predictor of mortality

Receiver operating characteristic curve (Fig. 2) showed a greater area under the curve for the plasma BNP level than for the APACHE II score, confirming a significantly better prognostic value of BNP level in predicting mortality.

### 3.5. Cutoff values of independent predictors for death in sepsis group

The cutoff value for death prediction (Table 3) was determined. The sensitivity and specificity were also shown in Table 3.

### 3.6. Correlation between plasma BNP level and APACHE II score

The correlation between BNP level and APACHE II score in each group was shown (Table 4), with positive correlation between BNP and APACHE II score in each group.

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**Table 2** Positive detection rates in patients with sepsis, SIRS, or non-SIRS

<table>
<thead>
<tr>
<th>Grouping</th>
<th>n</th>
<th>BNP ≥ 100 pg/mL (%)</th>
<th>BNP ≥ 500 pg/mL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-SIRS</td>
<td>360</td>
<td>38.6</td>
<td>11.1</td>
</tr>
<tr>
<td>SIRS</td>
<td>313</td>
<td>73.2 **</td>
<td>44.4 **</td>
</tr>
<tr>
<td>Sepsis</td>
<td>327</td>
<td>62.1 ***</td>
<td>29.7 ***</td>
</tr>
</tbody>
</table>

\(^{***}P < .01\), compared with SIRS.

\(^{**}P < .001\), compared with SIRS.

\(P < .01\), compared with non-SIRS.

\(P < .001\), compared with non-SIRS.

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**Fig. 1** The 28-day mortality in non-SIRS, SIRS, sepsis group. Asterisk indicates that the data were compared with non-SIRS group; **\(p < .01\); ***\(p < .001\).

**Fig. 2** Receiver operating characteristic curves for BNP and APACHE II score in sepsis group.
4. Discussion

Many diseases may induce abnormal body temperature (the body temperature >38°C or <36°C), fast breathing frequency (respiratory rate >30 times per minute), fast pulse rate (pulse rate >90 times per minute), abnormal leukocytes (>12 000/L or <4000/L) in emergency department. The occurrence of 2 or more aforementioned manifestations is defined as SIRS [3], which aims to remind clinicians to pay attention on those patients who had potential serious diseases. However, since the introduction of SIRS in 1991, relatively big disputes still existed. The focus of the dispute is its extremely high sensitivity and poor specificity, and it seems that there is no guiding significance for the clinical discrimination of dangerous and serious patients.

The researchers have long been searching for the biological markers that can distinguish SIRS patients who may develop and experience aggravation from large amount of SIRS patients. We measured the plasma BNP levels in SIRS, septic, and non-SIRS patients and compared its positive rate and the effects on prognosis to search sensitive biological parameters for the evaluation of the prognosis of SIRS and septic patients.

4.1. Positive detection rate of BNP and its clinical significance

Plasma BNP level is one of the biological parameters for the clinical evaluation of cardiac functions [7]. The brain natriuretic peptide was previously used for the detection, stratification, and prognosis of congestive heart failure with high sensitivity and specificity [1-2]. Apart from the increase in ventricular wall tension that leads to BNP release, other factors such as catecholamines, renal failure, central nervous system disease, and up-regulation of cytokines can also induce increased BNP levels.

There are many studies that relate BNP levels to sepsis and septic shock, and these studies mainly focused on hospitalized patients in intensive care unit. Most of these studies strictly excluded situations that affect BNP levels such as congestive heart failure, chronic renal failure, and others. In the clinical practice of emergency treatment, many critical ill patients may have several kinds of fundamental chronic diseases, and they seek emergency treatment just due to short-term episode of one of the diseases. Conclusions from the aforementioned studies cannot be really applied in clinical treatments of these patients. Therefore, their support in the guidance of clinical emergency practices still needs further investigations. Rivers et al [3] used septic or septic shock patients in the emergency department as subjects and found that the positive rate for BNP (>100 pg/mL) was 42% in sepsis patients and 69% in those patients with septic shock, indicating that the rate of BNP in septic patients was rather high. We investigated those patients who had many fundamental diseases and might experience aggravation due to some inducing factors such as infections together with sepsis or SIRS. If the clinical significance of positive rate of BNP in septic and its prognostic values to death in these patients can be clarified, they will actively influence the clinical emergency treatment.

In this study, the positive detection rate of BNP (≥100 pg/mL) was 73.2% in SIRS group, 62.1% in sepsis group, and 38.6% in non-SIRS group (Table 2). The positive detection rate in SIRS and sepsis groups were significantly higher than in non-SIRS group ($P < .01$). The positive detection rate of BNP was 11.1% in non-SIRS group, 44.4% in SIRS group, and 29.7% in septic group, with significant differences among 3 groups ($P < .001$; Table 2). The patients with congestive heart failure identified by clinical trials was 4.7% in non-SIRS group, 28.1% in SIRS group, and 10.1% in sepsis group, significantly lower than the positive detection rates of BNP (≥100 pg/mL; $P < .001$ and $≥500$ pg/mL; $P < .01$, respectively), indicating that acute cardiac dysfunction might increase the positive detection rates of BNP in the following possible reasons.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Cutoff values of death within 28 days for septic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors</td>
<td>Cutoff value</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>113</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>21.5</td>
</tr>
</tbody>
</table>

PPV indicates positive predictive value; NPV, negative predictive value; AUC, area under receiver operating characteristic curve.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Correlation between BNP and APACHE II score</th>
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<tbody>
<tr>
<td>Group</td>
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</tr>
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<td>313</td>
</tr>
<tr>
<td>Sepsis group</td>
<td>327</td>
</tr>
</tbody>
</table>

group ($P < .01$). Although the relationship between BNP and APACHE II score seemed weak (the Spearman’s correlation coefficient $<0.3$), they had significant statistical value in all 3 groups ($P < .01$).
The incidence rates of cardiac dysfunction in patients with SIRS or sepsis significantly increased than that of non-SIRS patients. By echocardiographic examination, previous investigations have confirmed that the percentage of contractile dysfunction of cardiac muscle and increased BNP level in those patients with sepsis or septic shock was 44% [8]. However, no result has been reported for the percentage of cardiac dysfunction in SIRS patients. The mechanism for cardiac dysfunction and myocardial injury might be related to myocardial depressant factors in the circulation, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and others [9], which can inhibit the contractile functions of cardiac muscles and then decrease myocardial contractility and ejection capability but increase the ventricular wall tension, finally increasing BNP secretion. Meanwhile, these myocardial depressant factors are inflammatory mediators, which can damage cardiac muscle cells directly, leading to myocardial dysfunction.

Previous investigations have revealed that BNP level also increased significantly in those patients with severe sepsis or septic shock while without cardiac dysfunction [10], but the mechanism for BNP increase in these patients is still unclear.

4.2. Prognostic significance for BNP increase in the plasma of septic patients

The increase of BNP level in the plasma of septic patients is common, whether such increase is paralleled to the cardiac functions of sepsis and is a prognostic index for septic patients has been studied widely [3,8,10-14]. In these studies, some investigations found that BNP level was correlated with cardiac functions, whereas others proved to be not. The significance of BNP in the prognosis of septic patients is also disputable, and no definite result can be found until now. Furthermore, the criteria for the inclusion of patients and the indexes for the evaluations on cardiac functions and prognosis are also different in these investigations. Hence, these results cannot be subjected to aggregate analysis. Therefore, whether plasma BNP level is a prognostic factor for sepsis has not been determined.

In this study, the plasma BNP level was an independent predictor for the 28-day mortality in septic patients, which was positively correlated to APACHE II score. The area under the curve of receiver operating characteristic was higher in plasma BNP level than that of APACHE II score, indicating the significance of BNP level (113 pg/mL, with high sensitivity and low specificity) in the septic prognosis. Considering the low sensitivity and high specificity of APACHE II score, both of them can be combined for aggregate analysis on the septic prognosis.

Myocardial dysfunction is common in patients with sepsis, and it is the main reason leading to death. As previous investigations indicated, the different forms of contractile dysfunction in left ventricle occurred in 44% patients with severe septic and septic shock but no cardiac disease and chronic renal failure [8]. The cardiac dysfunction in sepsis is characterized by the decreases in contractile and diastolic functions of both cardiac ventricles, and the main reason for that is the myocardial inhibition. There are many inflammatory mediators in the circulation of patients with sepsis can induce myocardial inhibition such as prostaglandins, interleukins, platelet activating factor, histamine, and endorphin [15]. Among these factors, TNF-α and IL-1β play the core roles [9]. Tumor necrosis factor-α and IL-1β take rapid effects in myocardial inhibition and continually exert effects for several days [9,16,17]. If no proper intervention is performed timely, the patient’s conditions will aggravate and even cause death. The ventricular dysfunction in sepsis increases the ventricular wall tension and pressure and thus increases the plasma BNP level. In comparison to the traditional indexes for the evaluations on cardiac functions, plasma BNP level is more sensitive and correlated with the severity of sepsis, and thus, it is considered as a sensitive predictor of death.

5. Conclusion

The positive detection rate of BNP and 28-day mortality in SIRS and sepsis patients in emergency department increased significantly than that of non-SIRS patients. Furthermore, the BNP level was significantly correlated with APACHE II scores, both of which were independent predictors for the death of sepsis patients. Brain natriuretic peptide level of more than 113 pg/mL in septic patients is the prediction cutoff value that increase the 28-day mortality. The selected subjects had varied baseline conditions, and the conclusions may not be accurate for individuals.

References


