The Differential Diagnostic Value of Serum NT-proBNP in Hospitalized Patients of Heart Failure With Pneumonia

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Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) is considered as an effective predictor for patients with heart failure (HF), while a strong body of evidence has found its utility in inflammatory diseases. It is difficult to differentiate HF and HF coexisting with other inflammations by measuring NT-proBNP. The aim of this study was to estimate the differential diagnostic performance of serum NT-proBNP in hospitalized HF patients with pneumonia. A prospective study was launched. Sixty nine HF patients, 51 HF patients complicated with pneumonia, and 38 patients with pneumonia were enrolled. Serum NT-proBNP levels were measured on Roche Elecsys. X-ray and the European Society of Cardiology (ESC) diagnostic principles were adopted to identify patients with pneumonia and HF, respectively. The diagnostic performance of NT-proBNP was assessed by ROC. Serum

NT-proBNP [7,039(1,008–24,672) pg/ml] in patients of HF complicated with pneumonia was significantly higher than that in those of patients with single HF [3,147(616–24,062) pg/ml] or single pneumonia [911(98–3,812) pg/ml] ($P < 0.0001$). No correlation was found between the level of NT-proBNP and hospital stay. The area under ROC curve (AUC) of NT-proBNP for distinguishing patients of HF with pneumonia was 0.8082. At the level of 4,691 pg/ml, the optimal cutoff value, 74.5% sensitivity and 81.8% specificity of NT-proBNP were predicted. Evaluation of serum NT-proBNP is conducive for clinicians to identify patients of HF with pneumonia, but its poor efficacy in monitoring the curative therapy in this entire cohort is not recommended. *J. Clin. Lab. Anal.* 29:37–42, 2015. © 2014 Wiley Periodicals, Inc.

Key words: NT-proBNP; HF; pneumonia; differential diagnosis

INTRODUCTION

N-terminal pro-B-type natriuretic peptide (NT-proBNP), the inactive fragment of B-type natriuretic peptide (BNP), is well recognized as a useful and efficient predictor for cardiac diseases in both diagnosis and prognostic mortality. Elevated serum NT-proBNP has contributed to identify the ventricular systolic and diastolic dysfunction in various settings that increase cardiac stress and output, such as hypertension, cardiac arrhythmia, hyperthyroidism, renal failure, chronic obstructive pulmonary disease, pulmonary embolism, and interstitial lung disease, especially in heart failure (HF; (1–4)).

Interestingly, as a neurohormone mainly secreted by ventricular cardiomyocytes stretch and degraded by renal clearance, NT-proBNP has been found dramatically elevated in inflammatory cases such as community-acquired

infection, HCV infection, liver cirrhosis, sepsis, and septic shock, even in cases where cardiac and renal dysfunction are absent (5–9), leaving their coexisting conditions more confusing. Moreover, some other changes are also well-known to be associated with circulating NT-proBNP level. Aging, gender, and body mass index are supposed to be related to the baseline of NT-proBNP (10). It is

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commonly considered that greater NT-proBNP levels by increasing age are due to the age-related alterations in heart and renal metabolism. It is therefore more sophisticated but important for the clinicians to identify all these additional stimuli for the release of NT-proBNP. But on reconsidering, cutoff values for NT-proBNP adjusted by different complicities are probably badly needed and depend on clinical decision making.

Considering few data have elucidated the potential diagnostic value in hospitalized patients of pneumonia with or without HF, this prospective study was launched to evaluate serum NT-proBNP and its differential diagnostic potency in patients with pneumonia and HF.

MATERIALS AND METHODS

Study Population and Design

One hundred and fifty-eight patients were consecutively enrolled into this study according to clinical and laboratory criteria during May 2010 and June 2011. They were hospitalized in the cardiology and respiratory departments of The First Affiliated Hospital of Chongqing Medical University. These patients were classified into three groups: pneumonia, HF, and HF with pneumonia. The diagnosis of HF was established according to European Society of Cardiology (ESC) definition and pneumonia was diagnosed by the symptoms and X-ray. Patients less than 60-year-old or with serum creatinine more than 100 $\mu\text{mol/l}$ were excluded. Written informed consents were obtained from all participants and the study protocol was approved by the local ethics committee, which complies with the ethical guideline of the 1975 Declaration of Helsinki.

Data Collection

Demographic and clinical information as well as age, gender, temperature (T), respiratory rate (R), heart rate (HR), duration of hospital stay, and left ventricular ejection fraction (LVEF) were collected on the first day of hospitalization. Echocardiography was performed using a commercially available system to examine cardiac structure and function. On the first day of hospitalization, blood samples were taken and laboratory report was obtained. White blood cell count was performed on Sysmex XE-2100. NT-proBNP was measured by the electrochemiluminescence assay (Cobass E411, Elecsys Roche Diagnostics, Mannheim, Germany). The sensitivity of NT-proBNP measured by the electrochemiluminescence assay is 5 pg/ml. Serum creatinine was determined by Module DDP (Elecsys Roche Diagnostics, Mannheim, Germany). All samples were analyzed in 1 hr after sample collection.

Statistical Analysis

The processing of the results was performed with GraphPad Prism version 5.01. Variables were described as the median or mean $\pm$ standard deviation (SD) by dividing the study group into subgroups. Between-group comparisons of continuous variables underwent the Mann–Whitney U test or one-way analysis of variance as appropriate. The correlations between continuous variables are described by Spearman's rank correlation coefficients. Categorical variables of frequencies and percentages were analyzed by the chi-square test with the differences. In all tests, two-tailed P value <0.05 was considered significant. Receiver operator characteristic curve (ROC curve) were used to illustrate the capacity of NT-proBNP as a valuable diagnostic tool for patients of HF with pneumonia.

RESULTS

Patient Characteristics

Of the entire cohort of 158 cases, three groups were divided by simple HF group (69 cases), HF with pneumonia group (51 cases), and single pneumonia group (38 cases). There was no significant difference between the above groups in gender, age, temperature, heart rate, and creatinine. Difference was significantly observed in WBC between these three groups, intergroup analysis showed there was elevated WBC in all pneumonia groups (HF with pneumonia group ($P = 0.0158$) and simple pneumonia group ($P = 0.0135$), indicating that WBC was sensitive to reflect the inflammation of pneumonia, even in patients of HF, who were always supposed to be insensitive to stimuli. LVEF was also different between HF groups and pneumonia. It is interesting that LVEF in HF patients with or without pneumonia is reduced to the same degree compared with patients of pneumonia, suggesting that pneumonia does not contribute to left ventricular dysfunction. The clinical characteristics of these patients and the univariate associations of the clinical variables between groups are listed in Table 1.

Higher Level of Serum NT-proBNP in Patients of HF With Pneumonia

Interestingly, serum NT-proBNP was significantly increased to a higher degree with the median of 7,039 pg/ml among patients of HF complicated with pneumonia than patients with HF only (3,147 pg/ml in median). Patients with pneumonia with a relative increase of serum NT-proBNP were also observed. Significant difference was found between groups ($P < 0.0001$, Fig. 1), suggesting that NT-proBNP is sensitive to discriminate pneumonia from normal population and patients with HF.

TABLE 1. The Clinical Characteristics and Univariate Associations of the Clinical Variables Between Groups

	HF (<i>n</i> = 69)	HF complicated pneumonia (<i>n</i> = 51)	Pneumonia (<i>n</i> = 38)
Sex (M/F)	33/36	21/30	20/18
Age (years)	71.9 ± 9.2 73	4 ± 11.4	73.9 ± 11.0
HR (beats/min)	105.7 ± 23.7	108.3 ± 17.4	102.2 ± 20.2
<i>R</i> (beats/min)	22.7 ± 4.2	20.8 ± 1.9	23.0 ± 4.5
<i>T</i> (°C)	36.8 ± 0.7	37.9 ± 0.8	38.1 ± 0.8
WBC (10 ⁹ /l)	7.1 ± 2.6	13.4 ± 3.0	14.1 ± 3.4
In-hospital time (day)	10(2–39)	10(3–57)	13(4–61)
sCr (μmol/l)	75(39–95)	79(56–97)	74(35–91)
LVEF (%)	51(33–69)	54(31–68)	64.0(53–69)
NT-proBNP (pg/ml)	3,147(616–24,062)	7,039(1,008–24,672)	911(98–3,812)

Age, HR, RI, T, and WBC were listed by mean ± SD.

Fig. 1. Serum NT-proBNP levels in three groups of patients. Serum NT-proBNP [7,039(1,008–24,672) pg/ml] in HF with pneumonia was significantly higher than that in single HF group [3,147(616–24,062) pg/ml] or single pneumonia group [911(98–3,812) pg/ml]. Each data point represents an individual's data. A horizontal line denotes the median NT-proBNP for the group of patients.

Negative Correlation of NT-proBNP and LVEF in Patients of HF With Pneumonia

Since some data have evidenced the well-known correlation between NT-proBNP and LVEF in various cardiac

dysfunction settings, it was proposed that NT-proBNP is correlated to LVEF in pneumonia. However, no correlation of NT-proBNP and LVEF was found in the pneumonia group ($r = -0.5879$; $P = 0.0739$; Fig. 2A), whereas a notable negative correlation between NT-proBNP and LVEF was observed among patients of HF with ($r = -0.4906$; $P = 0.0024$; Fig. 2B) or without pneumonia ($r = -0.5348$; $P = 0.0003$; Fig. 2C). These findings suggest that the well-known association of NT-proBNP and LVEF may not be always true, at least in this cohort. However, as a potential inflammatory predictor, the potency of NT-proBNP can be brought into full play in such situations.

The Diagnostic and Predictive Value of NT-proBNP in Patients of HF With Pneumonia

The area under the ROC curve (AUC) with regard to diagnosis of HF with pneumonia was 0.8082 (95% CI: 0.7405–0.8409, $P < 0.0001$, Fig. 3). The cutoff value of NT-proBNP with the best diagnostic ability was 4,691 pg/ml, leaving a sensitivity of 74.5% and a specificity of 81.8%. Moreover, the predictive value of NT-proBNP was also evaluated by the duration of hospital stay. Unluckily, no correlation was found between NT-proBNP and days of hospital stay in this cohort (Fig. 4), indicating that NT-proBNP may be less efficient for monitoring therapeutic effect of HF treatment.

DISCUSSION

NT-proBNP is a pivotal member of cardiac endocrine, which regulates the hemostasis of circulating volume by mediating the balance of body fluid. A strong body of evidence has suggested the diagnostic and prognostic value of NT-proBNP in HF and other cardiovascular diseases, such as myocardial infarction, cardiac arrhythmia, and hypertension, whereas growing data have advocated its

Fig. 2. The correlation of serum NT-proBNP and LVEF in three groups: (A) HF ($n = 69$), (B) HF with pneumonia ($n = 51$), (C) pneumonia ($n = 38$). Spearman's rank correlation coefficient was used to assess correlations. P values are shown.

Fig. 3. The diagnostic and predictive value of serum NT-proBNP in patients of HF with pneumonia ($n = 51$). The cutoff value of NT-proBNP with the best diagnostic ability was 4,691 pg/ml.

elevation and potency in different sets of inflammations, such as HCV infection, respiratory tract infections, autoimmune disease, sepsis, and septic shock. Its underlying mechanism is still unclear. Recent studies have shown the oxidative stress, IL-1 β , IL-6, TNF- α , JAK/STAT, and TLR-4/NF-k β signaling may contribute to myocardial dysfunction (6–8), resulting in the increase of circulating

NT-proBNP in a reversible way. More importantly, this convertible elevation may cause a so-called “gray zones” of NT-proBNP (400–2,000 pg/ml), which has limited and confused the diagnosis and triage of patients. It is therefore conceivable to turn the sights into the potential of NT-proBNP in identification of all these confusing settings complicated with HF (11, 12).

This study has first found that the serum level of NT-proBNP was useful to distinguish patients of HF with pneumonia from those with HF alone or pneumonia alone. Patients of HF with pneumonia were observed with a conspicuously higher concentration of NT-proBNP than patients with single HF or pneumonia, indicating that NT-proBNP is sensitive and possibly helpful to capture and categorize patients in this complex situation. Our data are consistent with the report by Jensen et al. (13). The ROC curve revealed that the best cutoff value (4,691 pg/ml) exhibited a relatively good diagnostic value in the HF with pneumonia cohort.

Additionally, it has been unveiled that pneumonia, well recognized as the most common complication of HF, may have no significant impact on LVEF, while it has triggered a considerable increase in NT-proBNP level, leaving its median among these patients to the “gray zones,” which is similar to the report of Brueckmann et al. (14). Nevertheless, the more noteworthy elevation of NT-proBNP among patients of HF coexisting with pneumonia than

Fig. 4. The correlation between serum NT-proBNP levels and hospital stay in three groups. (A) HF ($n = 69$), (B) HF with pneumonia ($n = 51$), (C) pneumonia ($n = 38$). Spearman rank correlation coefficient was used to assess correlations.

patients simply with HF with the paralleling LVEF, hinting that the ability of diagnosis of NT-proBNP in complex settings coexisting with HF is associated with LVEF and a synergistic effect should be blamed for this distinct elevation when LVEF is reduced. Besides, in the similar LVEF settings, the overload of right ventricular and the consequently exaggerated hypoxia among patients of HF coexisting with pneumonia have probably induced the oversecretion of NT-proBNP (15). Furthermore, it is speculated that the relatively mild and short-term stimuli by inflammatory factors is transient and may not cause structural damages to ventricular myocardium. Consequently, the inflammatory burden and structural abnormality is probable to be “the two to tango” in the regulation of NT-proBNP. Moreover in this study, NT-proBNP was found to be irrelevant to the duration of hospitalized stay, suggesting its poor role in monitoring the curative effect of clinical therapy whether it is for HF, pneumonia, or HF with pneumonia. Despite several data have advocated the utility of NT-proBNP in the course of HF treatment (16, 17), it is still controversial that guidelines do not recommend this clinical behavior at present. In summary, assessment of serum NT-proBNP is helpful for clinician to identify patients of HF, pneumonia, and HF with pneumonia, but inefficient to monitor the curative effect of this entire cohort.

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CONFLICT OF INTEREST

None declared.

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