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Prognostic value of N-terminal pro-brain natriuretic peptide in hospitalised patients with community-acquired pneumonia

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ABSTRACT

Background The prognostic role of N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with community-acquired pneumonia (CAP) has not been evaluated. The aim of the present study was to investigate whether NT-proBNP level could predict mortality in hospitalised CAP patients.

Methods We performed a structured medical record review of all hospitalised CAP patients from May 2003 to October 2006, and classified patients into the 30-day survival and non-survival group. Data included demographic and clinical characteristics, and laboratory findings including NT-proBNP levels. The APACHE II scores, PSI (pneumonia severity index) and CURB65 (confusion, urea, respiratory rate, blood pressure and aged 65 or more) scores were calculated. Comparisons between survivors and non-survivors were made with χ^2, non-parametric tests and logistic regression and ROC analysis were used to compare the ability of NT-proBNP (adjusted for age, heart failure and creatinine), APACHE II, PSI and CURB65 to predict mortality.

Results Of 502 patients, 61 (12.2%) died within 30 days. NT-proBNP levels were measured in 167 patients and were significantly higher in non-survivors compared to survivors (median 841.7 (IQR 267.1—3137.3) pg/ml vs 3658.0 (1863.0—7025.0) pg/ml, p=0.019). NT-proBNP was an independent predictor of mortality (adjusted OR 1.53; 95% CI 1.16 to 2.02, p=0.002). The AUC for NT-proBNP was 0.712 (95% CI, 0.613 to 0.812), which was comparable to those of PSI (0.749, p=0.531) and CURB65 (0.698, p=0.693), but inferior to that of APACHE II (0.831, p=0.037). Adding NT-proBNP to APACHE II, PSI and CURB65 did not significantly increase the AUCs, respectively.

Conclusions NT-proBNP level is an independent predictor of mortality in hospitalised CAP patients. The performance of NT-proBNP level is comparable to those of PSI and CURB65 in predicting mortality.

INTRODUCTION

Community-acquired pneumonia (CAP) is a common and leading infectious cause of death throughout the world. Although the mortality rate in CAP patients has decreased with widespread use of antibiotic therapy, the mortality rate for hospitalised CAP patients ranges between 10% and 15%.[1 2] Several predictive systems have been developed to assist clinicians in predicting mortality and determining patient disposition, including the pneumonia severity index (PSI) and CURB65 (confusion, urea, respiratory rate, blood pressure and aged 65 or more) scores.[3–5] In addition, several serum biomarkers such as white blood cell (WBC) counts, C-reactive protein (CRP), d-dimer and procalcitonin have also been investigated as potential predictors of mortality of CAP.[6–10]

Recently, B-type natriuretic peptide (BNP) has been investigated as a predictive biomarker in CAP. BNP is composed of 32 amino acids and produced as a pre-prohormone protein, proBNP. In response to myocardial stretch, volume overload and elevation of end-diastolic pressure, proBNP is secreted from cardiac myocytes, and cleaved into an active BNP and an inactive N-teminal pro-B-type natriuretic peptide (NT-proBNP) which is composed of 76 amino acids. While biologically distinct, both BNP and NT-proBNP are usually used in the assessment of cardiac function and have an important role in the regulation of natriuresis, diuresis and vascular tone.[11–15] They have been studied for the diagnosis and prognosis of patients with congestive heart failure (CHF), myocardial infarction, pulmonary embolism and sepsis.[16–20]

In 2005 and 2008, Muller *et al*[21 22] first suggested that BNP might be useful in the risk stratification of CAP patients. They further hypothesised that elevated BNP levels in CAP patients might reflect the severity of pneumonia associated with an increase in pulmonary artery pressure, the secretion of proinflammatory cytokines and the existence of comorbidities such as heart failure and renal dysfunction. Yetkin *et al*[23] also reported a transient increase in BNP levels of CAP patients. However, we are unaware of any studies evaluating the relation between NT-proBNP and clinical outcomes in CAP patients. Based on these studies, we hypothesised that NT-proBNP might also have a predictive value for mortality in CAP patients.

METHODS

Study design

We performed a retrospective study based on data derived from electronic medical records. The study was conducted in the emergency department (ED) of a 960-bed academic urban tertiary-care hospital with an annual ED census of 65 000 patients. The department is staffed by emergency medicine and rotating residents and supervised by board-certified emergency physicians. This study was reviewed and approved by our institutional review board and was exempted by informed consent.

Study setting and population

We identified all patients with a principal diagnosis of pneumonia according to the International Classification of Diseases (ICD), 10th Revision codes J10.0–J18.9 from May 2003 to October 2006. The diagnoses of patients were determined by physicians from the emergency medicine and doctors in charge of patients on admission. They coded the patients according to the ICD 10. We reviewed the medical records of all patients coded with J10.0–J18.9, including length of stay, discharge from hospital, transfer to other hospital, x-ray findings and laboratory findings. Of these patients, hospitalised patients over 18 years presenting to the ED with a clinical diagnosis of CAP were eligible for enrolment.

Pneumonia was defined as symptoms of respiratory tract infection, the presence of an acute infiltrate on a chest radiograph and physical signs consistent with pneumonia on chest auscultation. Exclusion criteria were as follows: hospital-acquired pneumonia, transfer from other hospitals prior to admission, recent administration of antibiotics, presence of aspiration tendency, patients who left the hospital against medical advice and presence of other infectious diseases. If a patient was admitted more than once during a six-month period, we included only the first hospitalisation. To investigate the role of NT-proBNP as initial predictive tool for the mortality of CAP patients, we excluded factors with influence on the process of CAP.

Study protocol

Standardised extraction of demographic and clinical data from the electronic medical records was performed by trained data abstractors following the guidelines of Gilbert *et al*.[24] In our institute, the administration of antibiotics to patients with CAP was in accordance with the Infectious Disease Society of America (IDSA) clinical practice guidelines.[25–27]

Measurements

Data extracted from the electronic medical records included demographic characteristics, underlying diseases and laboratory findings. NT-proBNP was detected in EDTA plasma and an electrochemiluminescence immunoassay was used for NT-proBNP analysis (Roche Diagnostics, Mannheim, Germany). The EDTA sample for NT-proBNP measurement was taken within 24 hours, usually within 6 hours, after patients presented to the ED. If sampling time was 24 hours or more after ED admission, it was not included. The acute physiology and chronic health evaluation (APACHE) II, PSI and CURB65 score were also calculated. For calculating these severity scores, some missing data were considered normal. The primary outcome of the study was 30-day survival.

Data analysis

The study patients were divided into two groups based on whether they survived for at least 30 days. The survival group included patients who survived beyond 30 days and the non-survival group consisted of patients who died within 30 days of admission.

All statistical analyses were conducted using SPSS for Windows version 14.0. Continuous variables are presented as means ± standard deviations or median with interquartile range (IQR) as appropriate. Categorical variables are presented as an absolute value and percentages. The Student t test was used for continuous variables, and the χ^2 or Fisher's exact tests were used to compare categorical variables. NT-proBNP was log transformed to overcome its asymmetrical distribution.

Based on previous studies, several biological factors including age, gender, CHF and renal dysfunction are known to affect NT-proBNP levels. Therefore we performed multivariate logistic regression analysis with NT-proBNP as the dependent variable and age, CHF and creatinine level as independent variables. We then used receiver operating characteristic (ROC) curves to calculate the area under curve (AUC) for NT-proBNP for predicting mortality and compared it with the performance of APACHE II, PSI and CURB65 scores using Stata SE 9.2.

The independent predictive value of NT-proBNP for mortality was then determined using a logistic regression model that included those variables with a p value<0.2 on univariate analyses. Cut-off values for NT-proBNP were determined by ROC curve analysis and the sensitivity, specificity, positive predictive and negative predictive values for each cut-off value of NT-proBNP were investigated. A p value <0.05 was considered to be statistically significant.

RESULTS

During the study period, the total number of patients with ICD-10 codes J10.0–J18.9 was 1156. Among them, we extracted data on 978 patients over 18 years old with a clinical diagnosis of pneumonia. After excluding the appropriate patients the total number of study patients was 502 (figure 1).

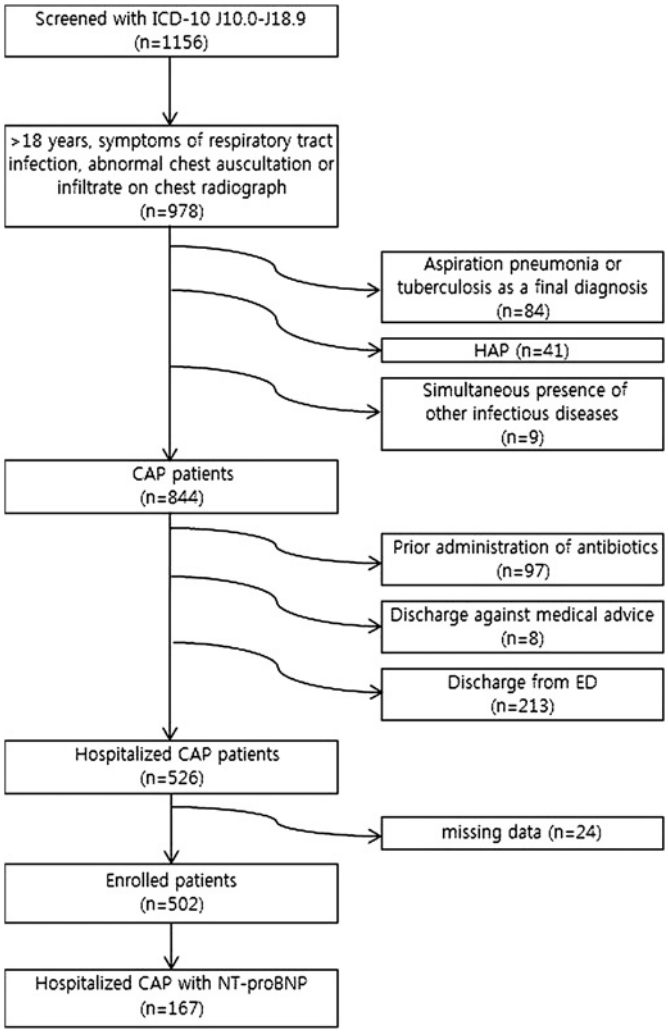

Figure 1 Inclusion and exclusion criteria. APACHE, acute physiology and chronic health evaluation; CAP, community-acquired pneumonia; CURB65, confusion,urea, respiratory rate, blood pressure and aged 65 or more; ED, emergency department; HAP, hospital-acquired pneumonia; PSI, pneumonia severity index.

Table 1 Baseline characteristics of the enrolled patients

	Survival group (n=441)	Non-survival group (n=61)	p Value
Mean age (years)	67.58 (SD 15.83)	77.03 (SD 8.84)	<0.001
Sex, No (%)			
Male	254 (57.6)	43 (70.5)	0.055
Female	187 (42.4)	18 (29.5)	
Underlying disease, No (%)			
Neoplastic	50 (11.3)	21 (34.4)	<0.001
Hepatic	33 (7.5)	7 (11.5)	0.309
CHF	25 (5.7)	7 (11.5)	0.093
Cerebrovascular	59 (13.4)	24 (23.0)	0.054
Renal	24 (5.4)	6 (9.8)	0.241
Diabetes	105 (23.8)	17 (27.9)	0.524
Hypertension	162 (36.7)	22 (36.1)	0.919
Cardiac (exception of CHF)	35 (7.9)	6 (9.8)	0.617
Tuberculosis	60 (13.6)	12 (19.7)	0.240
Asthma and COPD	68 (15.4)	5 (8.2)	0.174

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

Table 2 Severity risk classification of the enrolled patients

	Survival group (n=441)	Non-survival group (n=61)	Total (n=502)
CURB65 score, No (%)			
0	91 (20.6)	1 (1.6)	92
1	164 (37.2)	10 (16.4)	174
2	120 (27.2)	21 (34.4)	141
3	56 (12.7)	17 (27.9)	73
4	10 (2.3)	11 (18.0)	21
5	0 (0)	1 (1.6)	2
PSI grade, No (%)			
1	43 (9.8)	0 (0)	43
2	78 (17.7)	1 (1.6)	79
3	116 (26.3)	9 (14.8)	125
4	149 (33.8)	24 (39.3)	173
5	55 (12.5)	27 (44.3)	82
APACHE II, mean (SD)	10.88 (5.49)	19.33 (6.33)	502

APACHE, acute physiology and chronic health evaluation; CURB65, confusion, urea, respiratory rate, blood pressure and aged 65 or more; PSI, pneumonia severity index.

Of the enrolled patients, 61 (12.2%) were in the non-survival group. The baseline demographics of the study patients are shown in table 1. Both groups had similar underlying diseases except for neoplastic disease.

A significant difference between survivors and non-survivors was observed for APACHE II, PSI and CURB65 scores. Table 2 shows the mortality of patients in each class of PSI and score of CURB65. An increase in mortality was noted with higher PSI class and CURB65 score. The APACHE II score was also significantly higher in non-survivors compared to 30-day survivors.

NT-proBNP levels were measured in 167 patients (33.3%). NT-proBNP levels were significantly higher in non-survivors compared to 30-day survivors (median 841.7 (IQR 267.1–3137.3) pg/ml vs 3658.0 (1863.0–7025.0) pg/ml, p=0.019) (table 3). Other laboratory data of enrolled patients are shown in table 3.

In the logistic regression analysis, NT-proBNP was adjusted for variables with a p<0.2. NT-proBNP was identified as an independent prognostic factor for predicting mortality in hospitalised CAP patients (adjusted OR 1.53; 95% CI 1.13 to 2.06, p=0.006) (table 4).

In our study, significant correlations between NT-proBNP and potential confounding biological factors were observed as follows: age (r=0.33, p<0.001), CHF (r=0.21, p=0.007) and creatinine levels (r=0.39, p<0.001). However, the correlation between NT-proBNP and gender was not significant (p=0.841). On the basis of these correlations, we adjusted NT-proBNP for age, CHF and creatinine using logistic regression analysis. We then evaluated the predictive accuracy of NT-proBNP for

Table 3 Initial haematological and biochemical parameters

	Survival group (n=441) Mean (SD)	Non-survival group (n=61) Mean (SD)	p Value
Systolic BP (mm Hg)	136.9 (26.6)	126.4 (2.0)	0.005
Diastolic BP (mm Hg)	73.8 (14.8)	70.4 (16.8)	0.101
Pulse rate (beats/min)	103.5 (21.1)	105.3 (24.2)	0.545
Respiratory rate (breaths/min)	23.6 (6.0)	26.0 (7.9)	0.028
Body temperature (°C)	37.6 (1.1)	37.2 (0.9)	0.003
pH*	7.43 (0.07)	7.38 (0.14)	0.012
pCO_2* (mm Hg)	35.8 (9.1)	40.1 (22.0)	0.148
pO_2* (mm Hg)	66.0 (18.4)	56.8 (15.3)	<0.001
HCO_3* (mmol/l)	22.9 (3.8)	22.4 (5.4)	0.486
Haemoglobin (g/dl)	12.8 (2.0)	12.1 (2.1)	0.014
Haematocrit (%)	38.0 (5.8)	36.6 (6.5)	0.068
White blood cells (10^9/l)	12.8 (6.0)	14.4 (8.5)	0.144
Platelet (10^9/l)	266.7 (114.4)	279.0 (135.5)	0.500
Sodium (mmol/l)	136.0 (4.6)	134.4 (8.0)	0.147
Potassium (mmol/l)	4.0 (0.6)	4.1 (0.8)	0.497
Blood urea nitrogen (mg/dl)	18.8 (12.0)	28.9 (17.8)	<0.001
Creatinine (mg/dl)	1.2 (0.8)	1.3 (0.7)	0.154
C reactive protein† (mg/l)	13.6 (10.6)	15.0 (10.3)	0.334
Glucose (mg/dl)	163.1 (76.2)	165.4 (68.8)	0.825
NT-proBNP‡ (pg/ml)	841.7 (267.1-3137.3)	3658.0 (1863.0-7025.0)	0.019

Values except NT-proBNP are presented as the mean±SD.
*328 patients in the survival group and 59 patients in the non-survival group.
†396 patients in the survival group and 58 patients in the non-survival group.
‡NT-proBNP is presented as median with IQR, 134 in the survival group and 33 in the non-survival group. BP, blood pressure; pH, hydrogen ion concentration; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen; HCO_3, bicarbonate; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 4 Predictors of mortality in multivariate logistic regression analysis

Variables	Adjusted OR	95% CI	p Value
NT-proBNP	1.53	1.13 to 2.06	0.006
Neoplastic disease	6.24	2.12 to 18.36	0.001
Cerebrovascular disease	4.16	1.27 to 13.66	0.019

Adjustment for variables with p<0.2 in univariate analyses.

mortality using ROC curve analysis. The AUC of NT-proBNP was 0.712 (95% CI 0.613 to 0.812). The performances of predictive rules for mortality were as follows: APACHE II, 0.847 (95% CI 0.804 to 0.890); PSI, 0.795 (95% CI 0.742 to 0.848); CURB65, 0.764 (95% CI 0.703 to 0.825). A comparison between the performance of NT-proBNP at predicting mortality and predictive rules is shown in figure 2. The AUC of NT-proBNP was comparable to those of PSI (0.749, p=0.531) and CURB65 (0.698, p=0.693), but significantly inferior to that of APACHE II (0.831, p=0.037). The performance of APACHE II at predicting mortality was significantly higher than those of PSI (p=0.02) and CURB65 (p=0.004) (figure 3). Adding the NT-proBNP to APACHE II, PSI and CURB65 did not significantly increase the AUCs (figure 4).

Table 5 shows the sensitivity, specificity, positive predictive value and negative predictive value at different cut-off value of NT-proBNP. Using a cut-off value of 1795.5 pg/ml, sensitivity was 81.8% and specificity was 65.7%.

DISCUSSION

A major advance in medicine over the past decade has been the discovery and development of novel biomarkers aimed at improving the ability of clinicians to make a diagnosis and predict the prognosis of their patients. Owing to the high incidence and mortality rate of CAP, several biomarkers such as WBC, CRP, d-dimer and procalcitonin have been evaluated.[6–10] As one of the rapidly available and potentially useful biomarkers, we evaluated the role of NT-proBNP in predicting mortality in hospitalised CAP patients. To our knowledge, the present study is the first to investigate NT-proBNP as a predictor for mortality in CAP patients.

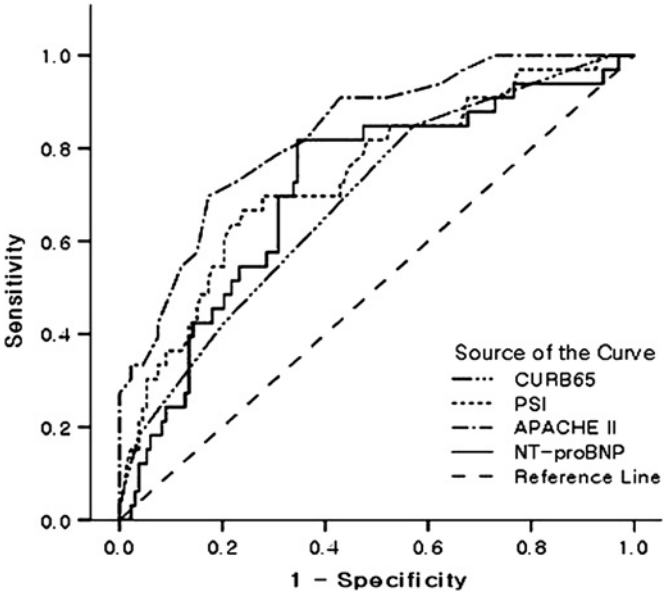

Figure 2 ROC curves for the NT-proBNP and predictive rules including APACHE II, PSI and CURB65 (n=167). The area under the ROC curves are 0.712 (95% CI, 0.613 to 0.812) for the NT-proBNP, 0.831 (95% CI 0.757 to 906) for APACHE II, 0.749 (95% CI, 0.652 to 0.846) for PSI and 0.698 (95% CI, 0.609 to 0.787) for CURB65. The AUC of NT-proBNP was comparable to those of PSI (p=0.531) and CURB65 (p=0.693), but significantly inferior to that of APACHE II (p=0.037).

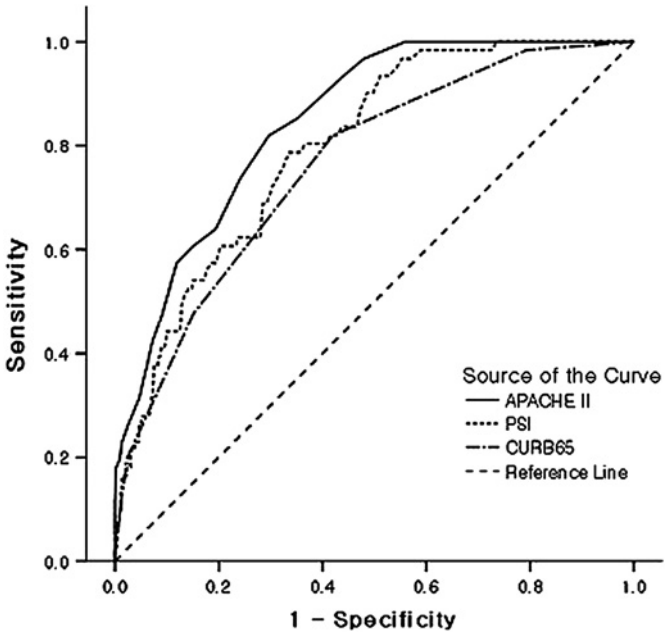

Figure 3 ROC curves for predictive rules (n=502). The area under the ROC curves are 0.847 (95% CI, 0.804 to 0.890) for APACHE II, 0.795 (95% CI, 0.742 to 0.848) for PSI, and 0.764 (95% CI, 0.703 to 0.825) for CURB65. The performance of APACHE II at predicting mortality was significantly higher than those of PSI (p=0.02) and CURB65 (p=0.004).

We found that NT-proBNP levels were significantly higher in non-survivors compared to survivors and that NT-proBNP might be an independent predictor of 30-day mortality in hospitalised CAP patients.

Our results lend further support to the notion that the natriuretic peptides may be useful as biomarkers that help to predict mortality in CAP patients. Previous studies have found that BNP is a powerful and independent predictor of mortality in CAP.[21–23] Like BNP, NT-proBNP has been identified as valuable biomarker that behaves very similarly to BNP in a variety of diseases. Several characteristics make NT-proBNP an attractive alternative to BNP. For example, NT-proBNP level in patients with heart and renal dysfunction rise more steeply than BNP. Also, NT-proBNP is larger, more rapidly detectable and more biologically stable than BNP and has a longer half-life.[28–30] With these in mind, we might infer that testing for NT-proBNP would have greater clinical utility than testing for BNP in assessing the prognosis of CAP patients. In a similar vein, Seino *et al*[31] previously demonstrated that NT-proBNP may be a more discerning biomarker for the evaluation of heart failure than BNP. However, we did not directly compare NT-proBNP with BNP in this study limiting our ability to comment on this issue.

This study suggests that the performance of APACHE II for predicting mortality is significantly superior to those of PSI and CURB65. As far as we know, these three predictive rules have not been simultaneously evaluated to predict mortality for CAP caused by heterogeneous pathogens. Several previous studies have compared the performance of different pairs of predictive

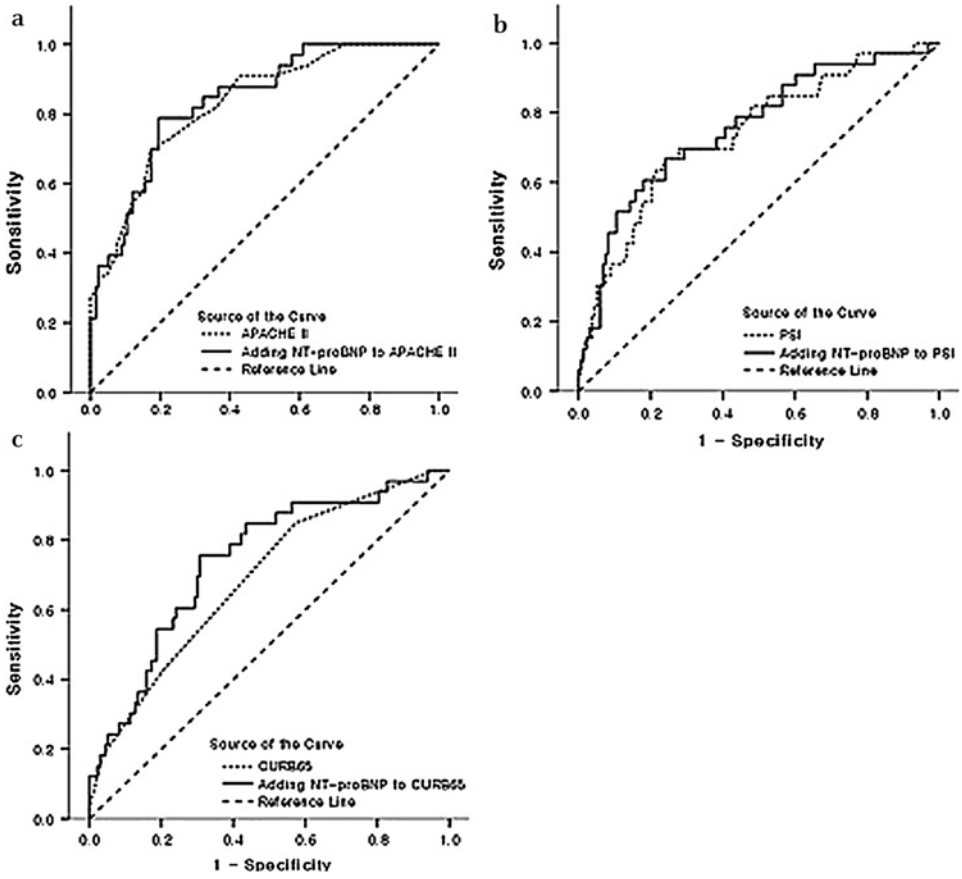

Figure 4 The incremental effect of NT-proBNP to the predictive rules using the area under the ROC curves (n=167). The area under the ROC curve was increased from 0.831 to 0.836 (p=0.623) for APACHE II (a), from 0.749 to 0.759 (p=0.555) for PSI (b) and from 0.698 to 0.735 (p=0.094) for CURB65 (c), respectively.

rules (such as PSI vs CURB65 and APACHE II vs CURB65) for predicting mortality in patients whose pneumonia was caused by a single pathogen.[32–34] Although the APACHE II was found to be more accurate than the PSI and CURB65, its calculation is more complicated and time-consuming. For these reasons, many clinicians, especially in the ED, cannot easily calculate the APACHE II scores of CAP patients, and therefore prefer to use the PSI or CURB65 for the evaluation of CAP. In order to be useful, any diagnostic modality or predictive tool should be both accurate and feasible in the clinical setting.

Although inferior to the more cumbersome APACHE II scoring system, the accuracy of NT-proBNP in predicting mortality in hospitalised CAP patients was comparable to those of PSI and CURB65. Thus measurement of NT-proBNP levels may be another method of predicting mortality in hospitalised CAP patients. However, PSI or CURB65 assessment has the advantage over biomarker in respect of cost and immediacy. Moreover, it was more available than NT-proBNP because NT-proBNP could not be measured as an emergency base in some institutions. We also investigated the incremental benefit of NT-proBNP on top of the currently existing predictive scoring system. Muller *et al*[22] reported that the combination of BNP and PSI significantly improved the prognostic accuracy of PSI alone. However, we could not find any significant improvements in accuracy when NT-proBNP was added to APACHE II, PSI, and CURB65. In contrast to the study conducted by Muller *et al*, our study included only hospitalised CAP patients with relatively higher PSI scores and small number of patients with NT-proBNP. Also, our study evaluated NT-proBNP which has some different characteristics from BNP. Because of these differences, we might infer that adding NT-proBNP to PSI might have minimal if any benefit. However, since the CURB65 system does not include any parameters that estimate heart function, the benefit of adding NT-proBNP to CURB65 score may be greater than for the other scoring systems.

The PSI and CURB65 system were originally developed to help identify low risk CAP patients who were safe for home discharge. In the present study the negative predictive value in patients with NT-proBNP levels <1795.5 pg/ml was 93.6. Moreover, there was a significant correlation between PSI, CURB65 and NT-proBNP (data not shown). These results suggest that an NT-proBNP level below this cut-off value might help clinicians in deciding who is safe to treat as outpatients.

LIMITATIONS

The present study has several limitations. First, the number of patients with NT-proBNP levels was only 167 and relatively

Table 5 Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value and negative predictive value at different cut-off value of NT-proBNP

Cut-off NT-proBNP	Sensitivity (%)	Specificity (%)	LR+	LR−	PPV (%)	NPV (%)
235.6 pg/ml	93.9	23.9	1.23	0.26	23.3	94.1
958.9 pg/ml	84.8	53.0	1.80	0.29	30.8	93.4
1795.5 pg/ml	81.8	65.7	2.30	0.32	37.0	93.6
2218.0 pg/ml	69.7	69.4	2.28	0.44	35.9	90.3

LR+, positive likelihood ratio; LR−, negative likelihood ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PPV, positive predictive value; NPV, negative predictive value.

smaller than those with APACHE II, PSI and CURB65 scores. It is possible that this introduced significant selection and/or spectrum bias since NT-proBNP levels may not be obtained in young, healthy, non-dyspnoeic patients without underlying cardiac or respiratory diseases. Second, the cardiac function of enrolled patients was not formally evaluated. Even though we adjusted for a history of CHF, we could not verify cardiac function. Third, the decision to admit patients with CAP was at the discretion of the attending physician and not standardised. Finally, our study was retrospective in nature and conducted at a single hospital and suffers from all of the limitations of this study design.

CONCLUSIONS

NT-proBNP level was found to be an independent predictor of mortality in hospitalised CAP patients. The performance of NT-proBNP level for predicting mortality was comparable to those of PSI and CURB65 scores. Although NT-proBNP was less accurate than the APACHE II score, it has the potential to be a useful biomarker for predicting mortality patients with CAP. In order to further investigate the predictive value of NT-proBNP, large randomised, prospective studies are needed.

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Competing interests None.

Ethics approval This study was approved by the Seoul National University Bundang Hospital Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

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