Evaluation of B-type natriuretic peptide as prognostic marker in patients with pneumonia: An observational study

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Abstract

Background: Pneumonia is the leading cause of death due to infection among the elderly in developed countries. We validated the usefulness of B-type natriuretic peptide (BNP) as a prognostic marker for pneumonia.

Methods: We carried out an observational study at Kanazawa Medical University Himi Municipal Hospital. We enrolled patients admitted between 1 January 2012 and 31 October 2016 with diagnoses of community-acquired pneumonia (CAP), non-CAP composed of aspiration pneumonia (AP) and healthcare-associated pneumonia (HCAP) whose BNP levels had been determined within the first 24 hours of admission. After enrollment, we collected baseline, demographic, clinical and laboratory characteristics, and outcome data. We followed

all patients until discharge. Primary outcome was defined as 30-day death. We applied univariate and multivariable Cox-regression analysis to each parameter to identify predictors of death for all included cases, CAP, and non-CAP.

Results: Of the 543 subjects included in the study, 205 were diagnosed with CAP and 338 with non-CAP. In the univariate analysis of the 543 subjects, mean BNP levels were associated with death (p = 0.0000); and in the multivariate analysis, BNP remained an independent predictor of mortality (cut-off points 220 pg/mL, hazard ratio (HR) 1.99, 95 % confidence interval (CI) 1.16-3.4, p = 0.01). A similar situation was found in univariate analysis of CAP and non-CAP (p = 0.0008, 0.0000, respectively), and in multivariable Cox-regression analysis of non-CAP (HR 2.27, 95 % CI 1.3-3.95, p = 0.004).

Conclusions: BNP level may be a useful single prognostic marker for AP or HCAP.

Key words: aspiration pneumonia, B-type natriuretic peptide, community-acquired pneumonia, healthcare-associated pneumonia, prognostic marker

Background

Pneumonia is the leading cause of death due to infection among the elderly in developed countries,[1,2] and Japan is no exception.[3] According to the list of surveys prepared by the Statistics and Information Department at the Japanese Ministry of Health, Labor and Welfare, pneumonia was the third leading causing of death in 2015, totaling 120953 cases with 97%, or 117707, of these being greater than 65 years of age.[3,4] In addition, according to the World Health Organization report of Global Health Estimates 2015, of the 56.4 million deaths worldwide in 2015, lower respiratory infections, including pneumonia, remained the most deadly communicable disease with 3.2 million deaths globally in 2015.[5] The percentage of the elder population (≥ 70 years old) in the total number of global deaths from lower respiratory infections is 45%, with high-income regions in particular reaching 86 %.[5]

The pneumonia severity index (PSI), confusion, urea plasma levels, respiratory rate, blood pressure, age greater than 65 years (CURB-65), and, especially in Japan, the A-DROP scoring system [age (men ≥ 70 years, women ≥ 75 years), dehydration (blood urea nitrogen (BUN) ≥ 21 mg/dl), respiratory failure (pulse oximetry ≤ 90 % or PaO_2 ≤ 60 Torr), orientation disturbance, and systolic blood pressure ≤ 90 mmHg)] are extensively used and validated tools in estimating the prognosis of patients with community-acquired pneumonia (CAP) despite their being difficult to calculate, prone to individual error, and partially dependent on individual impressions.[6] In addition, unfortunately, PSI or CURB-65 have not been validated in older adults, in whom assessment of mortality risk alone might not be adequate for the prediction of outcomes.[7] As such, a fast, simple, and reliable predictor is required for acute situations.

Recent research has suggested B-type natriuretic peptide (BNP), a 32-amino-acid polypeptide, as a prognostic factor for CAP.[1,8] We previously conducted a systematic assessment of BNP levels as a prognostic marker for other types of pneumonia and reported that its levels may be a useful single prognostic marker for CAP and that a measured level of ≥ 224.1 pg/mL indicated an increased risk for death.[9] Our continued research included a systematic assessment of BNP levels as a prognostic marker for pneumonia to validate its effectiveness.

Methods

Study design

Study design was as described previously in this continuation of an observational study carried out at Kanazawa Medical University Himi Municipal Hospital (a 250-bed community hospital),[9] which is only public hospital in Himi city, Toyama Prefecture. As of October of 2016, aging rate of the city, namely the percentage of people 60 years old or over in the total population, is 37 % and is proceeding at a faster pace than ever.[10] This study was approved by the Kanazawa Medical University Himi Municipal Hospital ethics committee (approval number 48), and carried out in conformance with the principles of the Declaration of Helsinki. Both verbal and written informed consent were obtained from all participating patients upon admission.

Data collection

Data collection was as described previously.[9] Before starting this research, all physicians at our hospital had been asked to measure BNP levels on admission for all patients diagnosed with pneumonia. Data were collected by reviewing electronic medical records held at our hospital, and we enrolled all patients diagnosed with pneumonia and admitted to our hospital between 1 January 2012 and 31 October 2016 whose BNP

levels had been determined in the first 24 hours of admission.

All patients were subjected to initial clinical assessment, including medical history, physical examination, electrocardiogram, pulse oximetry, blood tests, including arterial blood gas analysis (when indicated), blood culture (when indicated), chest radiograph, and chest computed tomography (CT).

After enrollment, we collected baseline, demographic, clinical and laboratory characteristics, and outcome data, including levels of suspected prognostic markers for pneumonia proposed in previous papers.[11-17] All patients received follow up until discharge.

The inclusion criteria were patients diagnosed with CAP, aspiration pneumonia (AP), and healthcare-associated pneumonia (HCAP). It was reported that 63.5 % of HCAP had AP, AP was associated with poor outcomes, and was considered a major characteristic of HCAP.[18] As such, we tentatively defined AP and HCAP as non-CAP. The exclusion criteria were patients diagnosed with other types of pneumonia or pneumonia with acute heart failure (PAHF), to remove the factor of heart failure for elevation of BNP levels, age less than 18 years, obvious traumatic cause of dyspnea, and patients who requested an early transfer to another hospital. Patients judged not to have been suffering from pneumonia after admission were also excluded.

Measurement of BNP

Measurement of BNP was as previously described.[9] BNP was detected in EDTA plasma samples using a fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA). The precision, analytic sensitivity, and stability of the system have been described previously.[9] Briefly, the coefficient of variation within a given assay has been reported to be 9.5 %, 12.0 %, and 13.9 % for levels of 28.8, 584.0, and 1180.0 pg/mL, respectively, while the coefficient of variation

between assays is 10.0 %, 12.4 %, and 14.8 %, respectively, for the same levels.

Definition

Definition and classification of each type of pneumonia were as described previously.[9] AP diagnosis followed Japanese Respiratory Society guidelines for the management of hospital-acquired pneumonia.[19] HCAP was defined according to the 2011 Japanese Respiratory Society guidelines for the management of nursing- and healthcare-associated pneumonia.[20] Additionally, we tentatively based the diagnosis of PAHF on the above-mentioned definition, as previously described, with reference to the Framingham scale.[21] Cardiologists with years of experience perform the diagnosis of acute failure using echocardiography in all suspected cases of PAHF. Patients that did not meet the criteria for AP, HCAP, or PAHF were classified into CAP. Patients meeting the diagnostic criteria for both HCAP and AP were classified as HCAP, and patients that met the diagnostic criteria for both PAHF and other pneumonias were classified as PAHF.

Statistical analysis

All patients were properly started empiric therapy based on Sanford Guide, afterwards they were performed definitive therapy. Primary outcome was defined as 30-day death.

We expressed categorical variables as number and percentage, and continuous variables as mean and standard deviation. Variables are given in parentheses when data were missing for a parameter. Normal distribution of continuous variables was assessed by Kolmogorov-Smirnov test. Univariate analysis was applied for comparison of baseline, demographic, clinical, laboratory characteristics and outcome data to both CAP and non-CAP cases. Logistic regression models were employed to estimate the potential clinical relevance of biomarker measurements.

Potential confounding variables were entered into the univariate model for comparison between survival and non-survival groups, and significant variables ($p < 0.001$) were added to a multivariable model. Univariate analysis applied Student's t-test for continuous variables and chi-squared or Fisher exact test was employed for categorical variables.

We applied Cox-regression analysis to identify predictors of death in multivariable analysis, and a BNP level cut-off point was set to ensure a mean level in all included cases. We first applied univariate and multivariable analysis to all included cases; and if BNP remained an independent predictor of death in multivariable analysis, we applied the same analysis to CAP and non-CAP. Additionally, we assessed potential for different BNP and risk stratification tools to predict 30-day mortality by comparing receiver operating curve characteristics (ROCs), and cutoff values were calculated by maximizing the product of sensitivity and specificity. STATA® software package (version 10; STATA Corp LP) was used for statistical analyses. A statistical two-tailed significance level of 0.05 was used and all hypothesis testing was two-tailed.

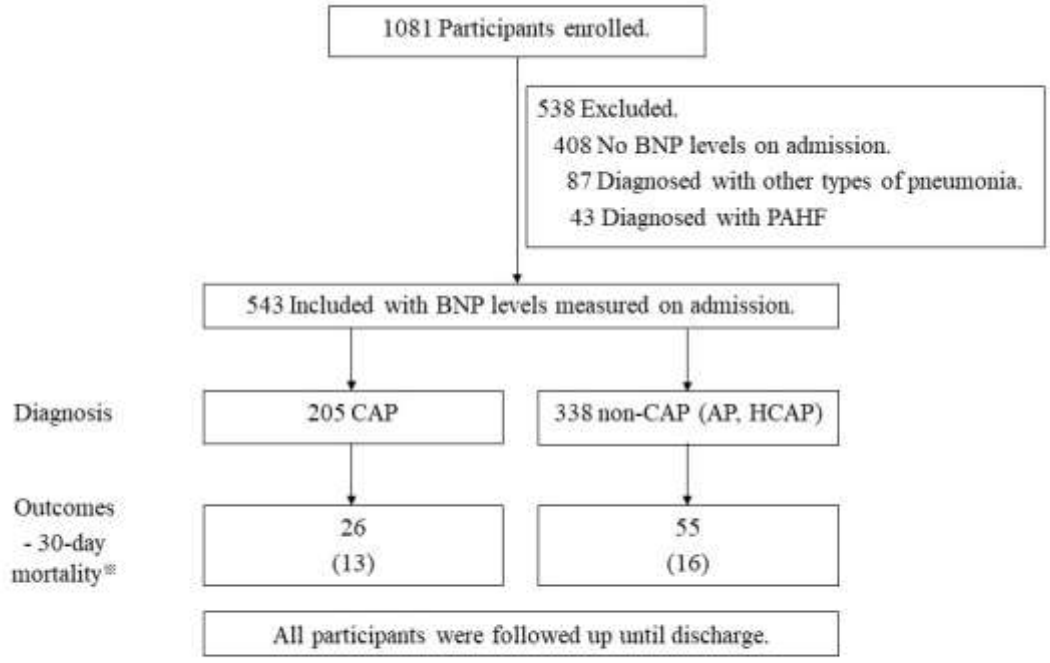
Results

Baseline characteristics

A total of 1081 patients were diagnosed with pneumonia during the period of this study. Of these, 408 were excluded as BNP levels were not measured within the first 24 hours of admission, 87 were diagnosed with other types of pneumonia, and 43 were diagnosed with PAHF. A total of 538 patients were excluded. No statistical difference was found in the clinical and laboratory findings and in the frequency of pneumonia subgroups between the excluded 538 and remaining included 543. Of 543, 205 were diagnosed with CAP, and 338 with non-CAP. The number of deaths was 26

and 55, respectively (mortality was 13 % and 16 %, respectively) (Figure 1). Of 338 non-CAP, 42 were tested for swallowing disorders by otorhinolaryngologists, 150 were evaluated by speech-language-hearing therapists, and 119 were evaluated by nurses. Twenty-seven were excluded from testing because of poor general condition. Of 338 non-CAP, 195 were AP and 143 were HCAP. Additionally, 92 HCAP also had AP. Baseline, demographic, clinical, and laboratory characteristics and outcome data were obtained for all included patients; namely, CAP, and non-CAP (Table 1).

Figure 1. Patient enrollment and outcomes.



※ Data are presented as No. (%). BNP = B-type natriuretic peptides, CAP = Community-Acquired Pneumonia, AP = Aspiration Pneumonia, HCAP = Healthcare-Associated Pneumonia, PAHF = Pneumonia with Acute Heart Failure

Table 1. Baseline, demographic, clinical and laboratory characteristics for all included patients, CAP, and non-CAP.

Parameter	All included cases (n=543)	CAP (n=205)	non-CAP (n=338)
Males	328 (60)	121 (59)	207 (61)
Age (years old)	82.5 ± 9.8	80.5 ± 11.4	83.7 ± 8.4
Systolic blood pressure (mmHg)	120 ± 28.7	123.8 ± 28.8	117.7 ± 28.5
Diastolic blood pressure (mmHg)	67.8 ± 18.3	69.4 ± 18.5	66.8 ± 18.2
Heart rate (beats / min)	94.6 ± 22.6 (n=541)	96 ± 24.2 (n=204)	93.8 ± 21.6 (n=337)
Body temperature (℃)	37.3 ± 2 (n=542)	37.3 ± 2.9 (n=204)	37.4 ± 1.2
Respiratory rate (breaths / min)	27.2 ± 13.2 (n=150)	28.2 ± 14.8 (n=39)	26.9 ± 12.7 (n=111)
Pulse oxymetory (%)	89.1 ± 10.9 (n=542)	90 ± 11.3 (n=204)	88.6 ± 10.6
Leukocytes (cells × 10^3 / μL)	11.1 ± 7.9	10.7 ± 5	11.4 ± 9.3
Lymphocytes (cells × 10^3 / μL)	1.2 ± 0.9	1.1 ± 0.7	1.2 ± 1
Hemoglobin (g / dL)	12 ± 1.9	12.2 ± 1.9	11.9 ± 1.9
Platelet count (cells × 10^{10} / L)	22.4 ± 11.7	23 ± 14.7	22 ± 9.3

Albumin (mg / dL)	2.89 ± 0.59 (n=479)	2.95 ± 0.61 (n=172)	2.85 ± 0.57 (n=307)
Aspartate transaminase (IU / L)	36.2 ± 53.2 (n=542)	37.2 ± 69.6	35.7 ± 40.1 (n=337)
Alanine transaminase (IU / L)	23.5 ± 35.5	25.2 ± 47.5	22.5 ± 25.7
Total bilirubin (mg / dL)	0.79 ± 0.6 (n=537)	0.82 ± 0.47 (n=201)	0.78 ± 0.67 (n=336)
Lactate dehydrogenase (IU / L)	241.6 ± 134.1 (n=537)	254.4 ± 181 (n=202)	233.9 ± 94.9 (n=335)
Blood urea nitrogen (mg / dL)	25.2 ± 17.1	25.3 ±18.4	25.2 ±16.3
Albumin / Blood urea nitrogen	0.15 ± 0.09 (n=479)	0.16 ± 0.09 (n=172)	0.15 ± 0.08 (n=307)
Creatinine (mg / dL)	1.02 ± 0.89	1.13 ± 0.96	0.96 ± 0.84
Serum sodium (mEq / L)	137.3 ± 5.9	138.4 ± 4.7	136.6 ± 6.4
Serum potassium (mEq / L)	4.23 ± 0.67	4.2 ± 0.66	4.24 ± 0.67
Serum chloride (mEq / L)	101.8 ± 7	102.8 ± 5.2	101.2 ± 7.8
Serum calcium (mEq / L)	8.09 ± 0.62 (n=324)	8.21 ± 0.57 (n=119)	8.02 ± 0.63 (n=205)
Plasma glucose (mg / dL)	146.2 ± 67.9 (n=524)	143.3 ± 62.1 (n=198)	147.9 ± 71.3 (n=326)
C-reactive protein (mg / dL)	9.08 ± 7.22	9.88 ± 7.48	8.59 ± 7.02

BNP (pg / mL)	219.8 ± 387	206.3 ± 329.5	228 ± 418.3
PaO_2 (mmHg)	75.1 ± 40.7	69.7 ± 35	77.7 ± 43.1
	(n=262)	(n=85)	(n=177)
$PaCO_2$ (mmHg)	37.9 ± 10	36.9 ± 10	38.4 ± 9.9
	(n=262)	(n=85)	(n=177)
Diabetes mellitus	89 (19)	42 (21)	67 (20)
Metabolic acidosis	30 / 262 (11)	9 / 85 (11)	21 / 177 (12)
Disseminated intravascular coagulation	25 (5)	8 (4)	17 (5)
Bacteremia	12 / 207 (6)	4 / 77 (5)	8 / 130 (6)
Septic shock	36 (7)	6 (3)	30 (9)
Orientation disturbance	158 (29)	37 (18)	121 (36)
Pneumonia: > 3 lobes of lung	239 (44)	91 (44)	148 (44)
Chronic obstructive pulmonary disease	159 (29)	65 (32)	94 (28)
Pleural effusion	202 (37)	63 (31)	139 (41)
Dyspnea	165 (30)	72 (35)	93 (28)
Malignancy	30 (6)	16 (8)	14 (4)
PaO_2 / FiO_2 <200	39 / 262 (15)	11 / 85 (13)	28 / 177 (16)
Hospitalization (days)	23.6 ± 19.1	20.1 ± 17	25.7 ± 20.1

Data are presented as mean ± SD or No. (%) as appropriate. CAP = Community-Acquired Pneumonia, BNP = B-type Natriuretic Peptides.

Missing data were confirmed for parameters that the physicians failed to confirm or measure. BNP levels of 543 patients were 219.8 ± 387 pg/mL. Comparison of CAP with non-CAP revealed significant differences in age, septic shock, orientation disturbance, pleural effusion, hospitalization, and measured levels of systolic blood pressure, hemoglobin, creatinine, serum sodium, serum chloride, serum calcium and C-reactive protein ($p < 0.05$).

Prediction of death in analysis

In the univariate analysis of all included patients, disseminated intravascular coagulation (DIC), septic shock, orientation disturbance, and pleural effusion, along with measured levels of BNP ($p < 0.001$), systolic blood pressure, diastolic blood pressure, body temperature, pulse oximetry, hemoglobin, albumin, lactate dehydrogenase, BUN, albumin / BUN, creatinine and serum potassium were associated with death (Table 2). In multivariable Cox-regression analysis, BNP (cut-off points 220 pg/mL, HR 1.99, 95 % CI 1.16-3.4, $p = 0.01$), orientation disturbance, pleural effusion, DIC, and measured levels of systolic blood pressure remained independent predictors of death (Table 2).

Table 2. Prediction of Death in Univariate and Multivariable Cox-Regression Analysis: all included patients.

Univariate Analysis			
Parameter	Survivors (n=462)	Non-survivors (n=81)	*p*-Value
Males	272 (59)	56 (69)	0.08
Age (years old)	82 ± 10.1	85 ± 6.8	0.01

Systolic blood pressure (mmHg)	122.4 ± 27	106.2 ± 33.9	< 0.001
Diastolic blood pressure (mmHg)	69 ± 17.3	60.7 ± 22.4	< 0.001
Heart rate (beats / min)	94.4 ± 21.5 (n=460)	95.9 ± 28.4	0.6
Body temperature (℃)	37.5 ± 1.1	36.4 ± 4.4 (n=80)	< 0.001
Respiratory rate (breaths / min)	25.8 ± 10.1 (n=112)	31.5 ± 19.4 (n=38)	0.02
Pulse oxymetory (%)	90.6 ± 6.3 (n=461)	80.6 ± 22	< 0.001
Leukocytes (cells × 10^3 / μL)	11.3 ± 8.2	9.9 ± 5.9	0.14
Lymphocytes (cells × 10^3 / μL)	1.2 ± 0.9	1 ± 1	0.17
Hemoglobin (g / dL)	12.2 ± 1.9	11.1 ± 2.2	< 0.001
Platelet count (cells × 10^{10} / L)	22.7 ± 12	20.8 ± 9.8	0.18
Albumin (mg / dL)	2.94 ± 0.57 (n=406)	2.62 ± 0.62 (n=73)	< 0.001
Aspartate transaminase (IU / L)	33.2 ± 36.5	53.8 ± 105.8 (n=80)	0.001
Alanine transaminase (IU / L)	22.8 ± 33	27.7 ± 47.6	0.25
Total bilirubin (mg / dL)	0.8 ± 0.61	0.77 ± 0.56	0.7

	(n=456)		
Lactate dehydrogenase (IU / L)	230.5 ± 84.1	303.7 ± 275.2	< 0.001
	(n=456)		
Alkaline phosphatase (IU / L)	297.7 ± 188.1	312.3 ± 158.4	0.6
	(n=299)	(n=50)	
Blood urea nitrogen (mg / dL)	23.1 ± 14.2	37.2 ±25.5	< 0.001
Albumin / Blood urea nitrogen	0.16 ± 0.09	0.1 ± 0.07	< 0.001
	(n=406)	(n=73)	
Creatinine (mg / dL)	0.97 ± 0.78	1.33 ± 1.32	< 0.001
Serum sodium (mEq / L)	137.4 ± 5.4	136.5 ± 8.1	0.22
Serum potassium (mEq / L)	4.19 ± 0.58	4.46 ± 1	< 0.001
Serum chloride (mEq / L)	101.9 ± 6.8	101.7 ± 8.1	0.85
Serum calcium (mEq / L)	8.09 ± 0.6	8.02 ± 0.75	0. 49
	(n=282)	(n=42)	
Plasma glucose (mg / dL)	144 ± 64.6	158 ± 83.6	0.09
	(n=444)	(n=80)	
C-reactive protein (mg / dL)	8.82 ± 6.91	10.5 ± 8.71	0.05
BNP (pg / mL)	181.6 ± 302.2	437.5 ± 657.5	< 0.001
PaO_2 (mmHg)	73.2 ± 32	81.9 ± 62.9	0.16
	(n=205)	(n=57)	

$PaCO_2$ (mmHg)	37.7 ± 9.4 (n=205)	38.6 ± 11.8 (n=57)	0.55
Diabetes mellitus	89 (19)	20 (25)	0.25
Metabolic acidosis	18 / 205 (9)	12 / 57 (21)	0.01
Disseminated intravascular coagulation	12 (3)	13 (16)	< 0.001
Bacteremia	9 / 175 (5)	3 / 32 (9)	0.4
Septic shock	18 (4)	18 (22)	< 0.001
Orientation disturbance	113 (24)	45 (56)	< 0.001
Pneumonia: > 3 lobes of lung	193 (42)	46 (58)	0.01
Chronic obstructive pulmonary disease	132 (29)	27 (33)	0.39
Pleural effusion	151 (33)	51 (63)	< 0.001
Dyspnea	131 (28)	34 (42)	0.01
Malignancy	18 (4)	12 (15)	< 0.001
PaO_2 / FiO_2 <200	22 / 204 (11)	17 / 57 (30)	< 0.001
Hospitalization (days)	24.2 ± 18.9	20.4 ± 20.1	0.1
Mortality	15 %		

Multivariable Cox-Regression Analysis

Parameter	Hazard Ratio (95 % CI)	*p*-Value
Disturbance of consciousness	1.91 (1.17-3.13)	0.01
BNP (≧ 220 pg / mL)	1.99 (1.16-3.4)	0.01

Pleural effusion	1.91 (1.12-3.25)	0.02
Systolic blood pressure (> 140 mmHg or ≦ 90 mmHg)	0.54 (0.3-0.97)	0.04
Disseminated intravascular coagulation	2.18 (1.03-4.61)	0.04

Data are presented as mean ± SD or No. (%) as appropriate. BNP = B-type Natriuretic Peptides.

In the univariate analysis of CAP and non-CAP, septic shock, orientation disturbance, pleural effusion, and measured levels of BNP ($p < 0.001$), systolic blood pressure, body temperature, pulse oximetry, albumin, BUN, albumin / BUN, creatinine, serum potassium, plasma glucose in CAP, DIC, septic shock, orientation disturbance, malignancy, and measured levels of BNP ($p < 0.001$), body temperature, pulse oximetry and lactate dehydrogenase were associated with death (Table 3).

Table 3. Prediction of Death in the Univariate and Multivariable Cox-Regression Analysis: CAP and non-CAP.

Univariate Analysis						
	CAP			non-CAP		
Parameter	Survivors (n=179)	Non-survivors (n=26)	*p*-Value	Survivors (n=283)	Non-survivors (n=55)	*p*-Value
Males	103 (58)	18 (69)	0.26	169 (60)	38 (69)	0.19

Age (years old)	79.8 ± 11.8	85.5 ± 6.4	0.02	83.5 ± 8.6	84.8 ± 7.1	0.3
Systolic blood pressure (mmHg)	126.5 ± 25.6	104.7 ± 40.8	< 0.001	119.8 ± 27.6	106.9 ± 30.5	0.002
Diastolic blood pressure (mmHg)	70.9 ± 16.9	58.9 ± 25.2	0.002	67.8 ± 17.4	61.5 ± 21.2	0.02
Heart rate (beats / min)	96.4 ± 21.1 (n=178)	93 ± 40.2	0.51	93.1 ± 21.7 (n=282)	97.2 ± 21	0.2
Body temperature (℃)	37.5 ± 1.1	35.3 ± 7.6 (n=25)	< 0.001	37.5 ± 1.1	36.9 ± 1.3	< 0.001
Respiratory rate (breaths / min)	25.5 ± 6.3 (n=30)	37.3 ± 27.7 (n=9)	0.03	25.9 ± 11.2 (n=82)	29.7 ± 16.2 (n=29)	0.16
Pulse oxymetry (%)	91.6 ± 6 (n=178)	79.7 ± 25.4	< 0.001	90 ± 6.5	81.1 ± 20.5	< 0.001
Leukocytes (cells × 10^3 / μL)	10.6 ± 4.8	11.4 ± 6.4	0.48	11.8 ± 9.8	9.2 ± 5.5	0.06
Lymphocytes (cells × 10^3 / μL)	1.1 ± 0.6	1.1 ± 1.4	0.92	1.3 ± 1.1	1 ± 0.8	0.1
Hemoglobin (g / dL)	12.4 ± 1.8	11.2 ± 2.2	0.003	12 ± 1.8	11.1 ± 2.2	0.001
Platelet count (cells × 10^{10} / L)	23.4 ± 15.3	20.7 ± 9.6	0.38	22.2 ± 9.2	20.8 ± 9.9	0.32
Albumin (mg / dL)	3.02 ± 0.57 (n=146)	2.53 ± 0.66	< 0.001	2.89 ± 0.56 (n=260)	2.67 ± 0.6 (n=47)	0.01
Aspartate transaminase (IU / L)	33.5 ± 43.5	62.7 ± 159.1	0.05	33 ± 31.4	49.5± 68.6 (n=54)	0.46

Alanine transaminase (IU / L)	24 ± 43.2	33.6 ± 71	0.34	22 ± 24.4	25 ± 31.6	0.44
Total bilirubin (mg / dL)	0.81 ± 0.43 (n=175)	0.88 ± 0.67	0.47	0.79 ± 0.7 (n=281)	0.72 ± 0.49	0.46
Lactate dehydrogenase (IU / L)	241.1 ± 99.3 (n=176)	344 ± 429.8	0.007	223.9 ± 72.3 (n=280)	284.7 ± 159.9	< 0.001
Alkaline phosphatase (IU / L)	304.6 ± 243.8 (n=104)	344 ± 215 (n=13)	0.58	294 ± 150.7 (n=195)	301.2 ± 135.1 (n=37)	0.79
Blood urea nitrogen (mg / dL)	21.5 ± 11.2	51.3 ± 32.4	< 0.001	24.1 ± 15.7	30.6 ± 18.3	0.007
Albumin / Blood urea nitrogen	0.18 ± 0.09 (n=146)	0.07 ± 0.05 (n=26)	< 0.001	0.16 ± 0.09 (n=260)	0.12 ± 0.07 (n=47)	0.003
Creatinine (mg / dL)	1.03 ± 0.82	1.79 ± 1.51	< 0.001	0.93 ± 0.75	1.12 ± 1.17	0.13
Serum sodium (mEq / L)	138.4 ± 4	138.6 ± 8.1	0.79	136.8 ± 6	135.7 ± 8	0.19
Serum potassium (mEq / L)	4.14 ± 0.49	4.68 ± 1.26	< 0.001	4.22 ± 0.63	4.35 ± 0.83	0.2
Serum chloride (mEq / L)	102.6 ± 4.5	104.3 ± 8.6	0.12	101.4 ± 7.8	100.5 ± 7.6	0.43
Serum calcium (mEq / L)	8.22 ± 0.56 (n=105)	8.06 ± 0.67 (n=14)	0.3	8.02 ± 0.61 (n=177)	8.01 ± 0.8 (n=28)	0.94
Plasma glucose (mg / dL)	137.4 ± 50.1	182.2 ± 106.8	< 0.001	148.2 ± 72.1	146.4 ± 67.9	0.86

	(n=172)			(n=272)	(n=54)	
C-reactive protein (mg / dL)	9.27 ± 6.77	14.01 ± 10.51	0.002	8.53 ± 6.99	8.88 ± 7.25	0.74
BNP (pg / mL)	177 ± 321.3	407.4 ± 320.7	< 0.001	184.6 ± 290	451.7 ± 769.5	< 0.001
PaO_2 (mmHg)	67.8 ± 32.8 (n=68)	77.5 ± 43 (n=17)	0.31	75.9 ± 31.3 (n=137)	83.7 ± 70.1 (n=40)	0.31
$PaCO_2$ (mmHg)	36.9 ± 9 (n=68)	37 ± 13.8 (n=17)	0.96	38.1 ± 9.6 (n=137)	39.3 ± 10.9 (n=40)	0.52
Diabetes mellitus	35 (20)	7 (27)	0.4	54 (19)	13 (24)	0.4
Metabolic acidosis	4 / 68 (6)	5 / 17 (11)	0.01	14 / 137 (10)	7 / 40 (18)	0.21
Disseminated intravascular coagulation	3 (2)	5 (19)	0.001	9 (3)	8 (15)	< 0.001
Bacteremia	3 / 68 (6)	1 / 9 (0)	0.4	6 / 107 (6)	2 / 23 (9)	0.63
Septic shock	1 (1)	5 (19)	< 0.001	17 (6)	13 (24)	< 0.001
Orientation disturbance	24 (13)	13 (50)	< 0.001	89 (31)	32 (58)	< 0.001
Pneumonia: > 3 lobes of lung	78 (44)	13 (50)	0.54	115 (41)	33 (60)	0.008
Chronic obstructive pulmonary disease	57 (32)	8 (31)	0.91	75 (27)	19 (35)	0.22
Pleural effusion	46 (26)	17 (69)	< 0.001	105 (37)	34 (62)	0.001
Dyspnea	58 (32)	14 (54)	0.03	73 (26)	20 (36)	0.11

Malignancy	11 (6)	5 (19)	0.02	7 (2)	7 (13)	< 0.001
PaO_2 / FiO_2 <200	6 / 68 (9)	5 / 17 (29)	0.02	16 / 137 (12)	12 / 40 (30)	0.005
Hospitalization (days)	19.5 ± 16.5	24.7 ± 19.8	0.15	27.1 ± 19.8	18.4 ± 20.1	0.003
Mortality	13 %			16 %		

Multivariable Cox-Regression Analysis

Type of pneumonia	Parameter	Hazard Ratio (95 % CI)	*p*-Value
CAP	Blood urea nitrogen (< 8 mg / dL or > 20 mg / dL)	7.35 (1.53-35.4)	0.01
	Pleural effusion	3.76 (1.31-10.8)	0.01
non-CAP	Malignancy	3.66 (1.56-8.6)	0.003
	BNP (≧ 220 pg / mL)	2.27 (1.3-3.95)	0.004
	Disseminated intravascular coagulation	3.14 (1.4-7.03)	0.006
	Septic shock	2.33 (1.2-4.49)	0.01
	Disturbance of consciousness	1.8 (1.01-3.21)	0.04

Data are presented as mean ± SD or No. (%) as appropriate. CAP = Community-Acquired Pneumonia, BNP = B-type Natriuretic Peptides.

In multivariable Cox-regression analysis, BUN and pleural effusion in CAP, BNP (cut-off points 220 pg/mL, HR 2.27, 95 % CI 1.3-3.95, $p = 0.004$), malignancy, DIC, septic shock and orientation disturbance in non-CAP remained independent predictors of death (Table 3).

Furthermore, for non-CAP, we summarized the area under the ROC curve (area under curve:

AUC) and likelihood ratios for different cut-off points (Table 4). Results showed BNP level to be accurate in predicting mortality (AUC = 0.66). Optimal cut-off point for predicting death was 202.8 pg/mL, with a sensitivity of 54.6 % and a specificity of 73.1 %. Negative predictive cut-off value was 2.03 %, and positive predictive cut-off value was 0.62 %.

Table 4. BNP thresholds to predict mortality. Sensitivity, specificity, positive likelihood ratio, negative likelihood ratio at different cut-off levels: non-CAP.

Cut-off BNP (pg / mL)	Sensitivity (%)	Specificity (%)	LR+ (%)	LR- (%)
100	72.7	51.9	1.51	0.53
200	54.6	72.8	2.00	0.62
202.8※	54.6	73.1	2.03	0.62
300	30.9	85.2	2.08	0.81

BNP = B-type natriuretic peptide, CAP = Community-Acquired Pneumonia, LR+ = positive likelihood ratio, LR- = negative likelihood ratio.

※The best calculated cutoff.

Discussion

In this cohort study of 543 patients with CAP and non-CAP, we determined the effectiveness of plasma BNP levels at admission in predicting unfavorable patient outcomes. We reported four major findings: significantly elevated BNP levels on admission in decedents with CAP and non-CAP; high admission BNP levels (≥ 220 pg/mL) as a predictor of non-CAP-related death; BNP level as an accurate predictor of mortality;

and an optimal cut-off point for the prediction of non-CAP-death of 202.8 pg/mL. In light of the high incidence of pneumonia and its prominent mortality rates, these findings may be of clinical significance.

The potential for BNP to serve as a predictor of CAP-related death seen in this study is in agreement with previous work.[1,8,22] On the other hand, there has been no comment in previous studies about its use as a prognostic marker in AP or HCAP; therefore, our results build on this finding. Our previous report showed that BNP is a prognostic marker in CAP group but not in HCAP group, however this result are inconsistent with it. The potential reason might be attributed to the lack of samples in previous study. We would like to convey two main messages to clinicians through this paper. First, BNP level alone can provide reliable data for a timely evaluation of prognosis in AP or HCAP patients admitted to the hospital, enabling clinicians can conduct proper empiric therapy on admission. Simple BNP level provides prognostic information equal to the complex variable severity index, whose laborious calculation is a major limitation for routine use. Of parameters excluding BNP which remain independent predictors of death in multivariable Cox-regression analysis of non-CAP, judgment of septic shock and orientation disturbance are based on subjective impressions; and calculation of DIC score is troublesome, making its routine use laborious. Second, while BNP is considered a marker for heart failure, it may also serve as a prognostic marker for pneumonia. From these points of view, BNP is an objective and reliable marker convenient for routine use.

The pathophysiologic mechanism of oversecretion of BNP has not as yet been completely clarified.[8] In general, BNP serves as an acute-phase reactant with an important role in regulating fluid volume, vascular pressure and electrolyte balance.[1,8,23-25] In addition, research has

suggested that hypoxia, leading to pulmonary vasoconstriction, pulmonary hypertension and right heart overload trigger BNP secretion.[1] On the other hand, other factors in BNP secretion have been identified as activation of proinflammatory cytokine and the sympathetic nervous system.[1,22] Consequently, in addition to the presence of disease-relevant co-morbidities and hypoxia, BNP may mirror inflammatory response.[1] We identified publications which report the mechanism of BNP secretion in CAP, however, we were unable to locate literature on the mechanism of elevation in patients with AP or HCAP.[1,8]

This study includes several limitations. In addition to this being a single center study, it is not possible to comment on BNP measurements in patients who were excluded as subjects. Further, our failure to measure BNP for all pneumonia patients prevents us from ruling out selection bias. In addition to measuring serum BNP levels in the acute phase, we should also have measured levels in the convalescent phase because a decrease in these levels post-treatment, which is compatible with control subjects, would show transiently elevated BNP levels in patients with pneumonia. Comparison of CAP with non-CAP for baseline, demographic, clinical, and laboratory characteristics and outcome data revealed significant difference in some variables. Finally, we were unable to demonstrate the mechanism of elevated BNP level in non-CAP.

As conclusions, BNP level may be a useful single prognostic marker for AP or HCAP. On the other hand, we will continue to collect more samples in the future to further confirm our findings. In addition, we will validate BNP secretion from lung in AP or HCAP making use of an animal model. Further studies are required to validate their utility in other types of pneumonia and to assess their application in clinical settings.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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