Utility of B-type Natriuretic Peptide in Patients with Acute Respiratory Distress Syndrome

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급성호흡곤란증후군 환자에 있어서 B-type Natriuretic Peptide의 유용성

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연구배경: B-type natriuretic peptide(BNP)는 심인성 및 다른 쇼크 상태를 포함하는 심혈관 질환에서 사망을 예측하는 좋은 인자 중의 하나로 알려져 있다. 그러나, 급성호흡곤란증후군환자에서 이런 관계가 잘 알려져 있지 않는 바, 저자들은 BNP가 급성호흡곤란증후군 환자에서 사망을 예측할 수 있는 지를 연구하였다.

방 법: 본 연구는 전향적 관찰로 시행되었다. 급성호흡곤란증후군으로 진단된 환자들에게 심초음파 검사를 시행한 후, 좌심실 구획률이 50% 미만이거나 확장성 심부전 양상을 보인 환자들을 제외하였다. 2003년 12월부터 2006년 2월까지 총 47명의 환자가 채택되었다. 등록된 환자들은 24시간 내로 BNP를 포함한 여러 검사실 수치를 얻었으며, APACHE (Acute Physiology and Chronic Health Evaluation) II 점수를 구하였다.

결 과: BNP와 APACHE II 점수 평균값은 생존자군과 사망자군에서 유의한 차의를 보였다(BNP: 219.5±57.7 pg/mL vs 492.3±88.8 pg/mL; p=0.013, APACHE II 점수: 17.4±1.6 vs 23.1±1.3, p=0.009). BNP 는 혈중 크레아티닌 수치와 양의 상관관계를 보였으나(r=0.374, p=0.01), 좌심실 구획률과는 유의한 관계가 없었다. Receiver operating characteristic 곡선상, BNP 수치를 585 pg/mL로 잡았을 때 사망을 예측하는데 있어서 94%의 특이도를 보였으며, APACHE II 점수의 경우에는 15.5를 기준으로 하였을 때 87%의 민감도를 보였다. 이 두 요소를 결합하여 '아파치II 점수+11×logBNP' 수치를 계산하여 기준점을 46.14로 했을 경우, 사망 예측에 있어서 민감도 63%, 특이도 82%의 결과를 얻을 수 있었다.

결 론: 좌심실 기능 부전을 보이지 않는 급성호흡곤란증후군 환자에서 BNP 수치는 생존자군과 사망자군에서 유의한 차이를 보였으며 사망을 예측할 수 있었다. 향후 급성호흡곤란증후군 환자에 있어서 BNP와 관련된 연구가 더 필요하다고 생각된다. *(Tuberc Respir Dis 2007; 62: 389-397)*

Key Words: Acute Respiratory Distress Syndrome (ARDS), B-type natriuretic peptide (BNP), Mortality, Prognosis.

INTRODUCTION

Among patients with congestive heart failure (CHF), B-type natriuretic peptide (BNP) concentrations reflect left ventricular end-diastolic pressure, left ventricular ejection fraction, and New York Heart Association heart failure class[1-5]. Assay for BNP has shown comparable accuracy in diagnosing, monitoring and establishing prognosis in patients with heart failure[6-9]. Although there were some reports that BNP can be elevated in patients with ARDS[10,11], little is known about the correlation between BNP and mortality in patients with ARDS. Some articles about BNP in patients with shock or respiratory failure were published, but the enrolled patients were not 100% ARDS patients[12-14]. Moreover, many of enrolled patients showed low ejection fraction, and this definitely affected the BNP concentration. We performed this study to see if BNP concentrations were elevated in patients with ARDS who had normal ejection fraction and evaluate the relationship between BNP and other variables. We also investigated if BNP and other variables could show difference between

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survivors and nonsurvivors and could predict mortality.

METHODS

Study Design

This was a prospective observational study. Consecutive patients admitted to medical, cardiac, and surgical intensive care units of The Kangnam St. Mary's Hospital who met inclusion criteria were enrolled. The study period was from December, 2003 to February, 2006. Written informed consent was obtained from either patient or next of kin. The Kangnam St. Mary's Hospital Institutional Review Board approved the study.

Patients

Patients were included who had acute respiratory failure (partial pressure of oxygen in arterial blood (PaO2) / fractional concentration of inspired oxygen (FiO2) ≤ 200 mmHg), bilateral infiltration on chest radiography, and no clinical evidence of increased left arterial pressure. Echocardiographic study was done and patients with ejection fraction (EF) lower than 50% or showing any features of diastolic dysfunction were ruled out. We also excluded patients younger than 18 years.

Measurements

BNP, PaO2, FiO2, C-reactive protein (CRP), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and EF were obtained within 24h hours at the time of enrollment. Patients were followed up, and 30-day survival was documented. Blood samples were obtained from peripheral blood. BNP was measured using the quantitative immuno-fluorescence assay Triage BNP (Biosite, San Diego, USA) on 5 ml of whole blood drawn in an ethylenediaminetetraacetic acid (EDTA) tube. This assay can detect BNP levels in the 5-5000 pg/mL range. APACHE II scores were calculated using data available from the 24-hr period at the time of enrollment. Transthoracic echocardiography is performed routinely in patients with ARDS. Systolic left ventricle (LV) dysfunction was defined as an EF below 50%. In patients without systolic LV dysfunction, diastolic dysfunction was defined as transmitral flow parameters consistent with one of the three patterns of diastolic dysfunction: impaired relaxation (LV peak E-wave velocity / LV peak A-wave velocity (E/A) < 1 and E-wave deceleration time (EDT) > 240 ms), pseudonormalization (1 < E/A < 2 and 150 < EDT < 200 ms) or restricted filling (E/A > 2 and EDT < 150 ms)[15]. Right ventricle (RV) dysfunction was defined as an RV-end diastolic area (EDA)/LV-EDA ratio grater than 0.6[16]. Pulmonary hypertension was defined when pulmonary regurgitation velocity > 2m/sec[17].

Table 1. Baseline characteristics of the study patients

Characteristic	Survivor (n=17)	Nonsurvivor (n=30)	p Value
Age, yr	65.5±4.8	65.8±2.3	0.943
Male gender, %	82 %	67 %	0.321
Pneumonia, %	65 %	73 %	0.500
Aspiration, %	24 %	7 %	0.170
Sepsis, %	12 %	43 %	0.026*
Renal failure, %	76 %	73 %	1.000
High PEEP, %	17 %	41 %	0.087
Postoperative, %	12 %	13 %	1.000
Medical/cardiac ICU, %	88 %	77 %	0.455
Pressor dependent, %	35 %	50 %	0.330
Ventilator dependent, %	82 %	100 %	0.042*

PEEP: Positive End-Expiratory Pressures
*: p<0.05

High Positive End-Expiratory Pressures (PEEP) was defined as more than 15 cmH_2O. The patients, researchers, physicians, and echocardiographers were blinded to the BNP concentrations.

Statistical Analysis

Independent samples T test was done to compare means of continuous variables. Chi-square test was used for analysis of categorical variables. Correlations between each variable were evaluated by bivariate analysis with Pearson correlation. Receiver operating characteristic (ROC) curves for BNP and APACHE II score were constructed to predict mortality. All statistical analyses were performed with SPSS software (Chicago, IL, USA).

RESULTS

Clinical characteristics and mortality

From 2003 December to 2006 February, 103 patients were diagnosed as ARDS. 17 patients refused to be enrolled. 14 patients were excluded because of failure of BNP sampling or echocardiographic examination within 24h hours of diagnosis. 25 patients showed LV dysfunction. So among 103 patients, 47 patients met inclusion criteria. 33 patients were on the intubated state during BNP sampling, 36 were during echocardiographic examination.

Seventeen patients were alive and thirty patients were dead at day 30. The baseline characteristics of the study group are shown in Table 1. Percentage

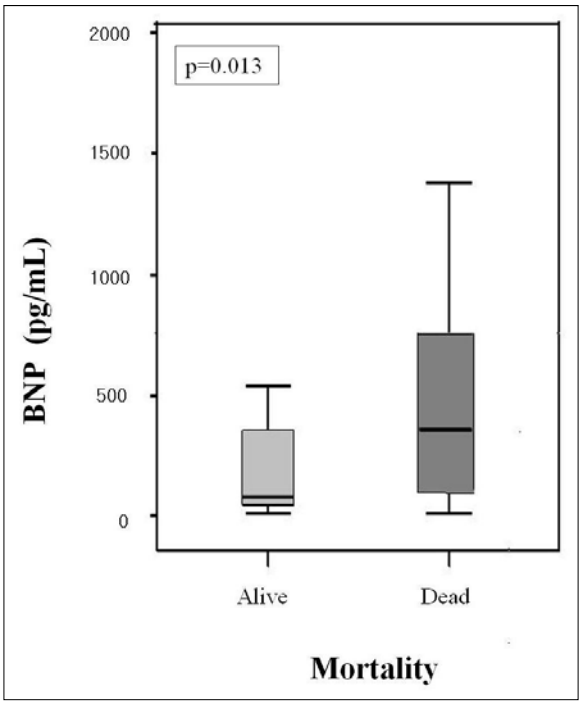

Figure 1. Box and whiskers plots of median B-type natriuretic peptide (BNP) concentrations among surviving patients vs. those dying during the study. The median BNP concentrations among those dying were significantly higher than those surviving (p = 0.013).

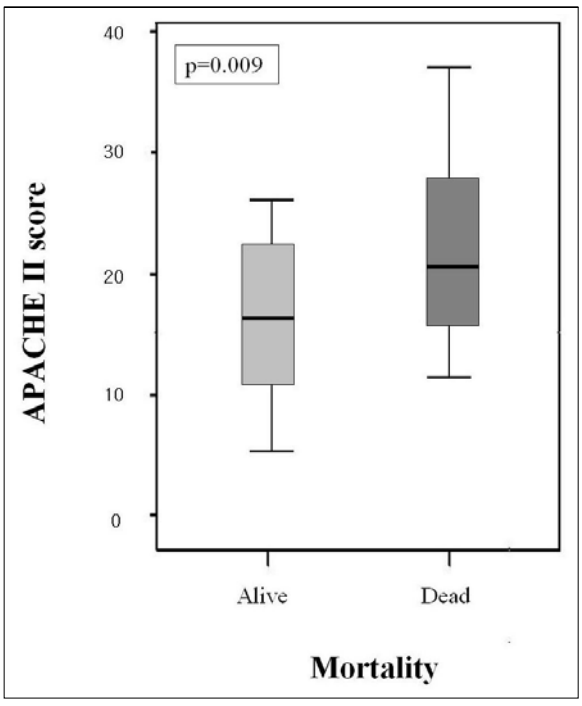

Figure 2. Box and whiskers plots of median acute physiology and chronic health evaluation (APACHE) II scores among surviving patients vs. those dying during the study. The median APACHE II scores among those dying were significantly higher than those surviving (p = 0.009).

Table 2. Comparison of parameters except APACHE II score and BNP

Characteristic	Survivor (n=17)	Nonsurvivor (n=30)	p Value
PaO2(mmHg)	75.1±7.1	78.9±4.3	0.625
PaO2/FiO2	103.1±9.8	100.7±4.9	0.827
CRP(mg/dL)	16.5±2.9	18.0±1.5	0.635
Cr(mg/dL)	1.39±0.11	1.54±0.21	0.624
EF, %	60.3±1.3	59.9±1.5	0.841
Pulmonary hypertension, %	27%	29%	1.000
Right ventricular dysfunction, %	20%	29%	0.493

PaO2: partial pressure of oxygen in arterial blood; FiO2: fractional concentration of inspired oxygen; CRP: C-reactive protein; Cr: creatinine; EF: ejection fraction

of sepsis and ventilator dependent showed significant differences (Sepsis, 12% vs 43%; p=0.026, Ventilator dependent, 82% vs 100%; p=0.042, respectively). Others did not differ significantly. BNP concentration and APACHE II score differ significantly between those who survived and those who died (BNP, 219.5 ± 57.7 pg/mL vs 492.3± 88.8 pg/mL; p=0.013, APACHE II score, 17.4 ± 1.6 vs 23.1 ± 1.3: p=0.009, respectively). Figure 1 and 2 show these differences. Parameters other than APACHE II score and BNP failed to show difference (Table 2). BNP concentration and EF were not different significantly between non-intubated and intubated group (BNP ; non-intubated : 331.7 ± 109.8 pg/mL vs intubated : 419.8 ± 77.3 pg/mL, p=0.517, EF ; non-intubated : 59.3 ± 2.1 % vs intubated : 60.3 ± 1.2 %, p=0.686).

Correlation

BNP concentration was correlated with serum creatinine level (r = 0.374, p = 0.010), but not with EF, age, PaO2, FiO2, PaO2/FiO2, CRP, and APACHE II score. APACHE II score was correlated with PaO2/FiO2 (r = -0.292, p = 0.047), Cr (r = 0.375, p = 0.009) (Table 3).

BNP concentration

In total enrolled patients, mean BNP concentration was 393 ± 63 pg/mL, and 66% of patients showed elevated BNP level (>100 pg/mL). We examined percentage of patients who are BNP > 100 pg/mL and mean BNP concentration between variable medical conditions(Table 4). These conditions can be causes of raised plasma BNP level[18]. Sepsis patients showed significantly increased percentage of BNP elevation, but mean BNP didn't differ significantly. In other conditions, although higher percentages were seen, p values were more than 0.05.

Table 3. Correlation between variables

Variables		Age	BNP	PaO2/FiO2	CRP	Cr	APACHE II	EF
BNP	r	0.086	1.000	-0.014	0.101	0.374	0.087	0.138
	p value	0.567	0.000	0.925	0.548	0.010†	0.562	0.355
APACHE II	r	-0.033	0.087	-0.292	0.212	0.375	1.000	0.079
	p value	0.824	0.562	0.047*	0.201	0.009†	0.000	0.597

BNP: B-type natriuretic peptide; PaO2: partial pressure of oxygen in arterial blood; FiO2: fractional concentration of inspired oxygen; CRP: C-reactive protein; Cr: creatinine; APACHE: Acute Physiology and Chronic Health Evaluation; EF: ejection fraction

* $p < 0.05$, † $p < 0.01$

Table 4. Comparison of B-type natriuretic peptide (BNP) concentration, as a function of medical conditions

Medical conditions		% of patients (BNP>100pg/mL)	p value	BNP(pg/mL) (Mean±SEM)	p value
ARDS		66		393±63	
Sepsts	Presence	87	0.040*	468±109	0.420
	Absence	56		358±77	
Renal fallure	Presence	71	0.289	446±77	0.159
	Absence	50		241±93	
Pulmonary hypertension	Presence	69	1.000	410±81	0.673
	Absence	65		350±87	
Right ventricular dysfunction	Presence	82	0.287	398±78	0.893
	Absence	61		378±86	
High PEEP	Presence	69	0.725	461±79	0.065
	Absence	58		196±59	
Vasopressor	Presence	71	0.477	410±91	0.772
	Absence	62		373±87	

BNP: B-type natriuretic peptide; PEEP: Positive End-Expiratory Pressures
* $p < 0.05$

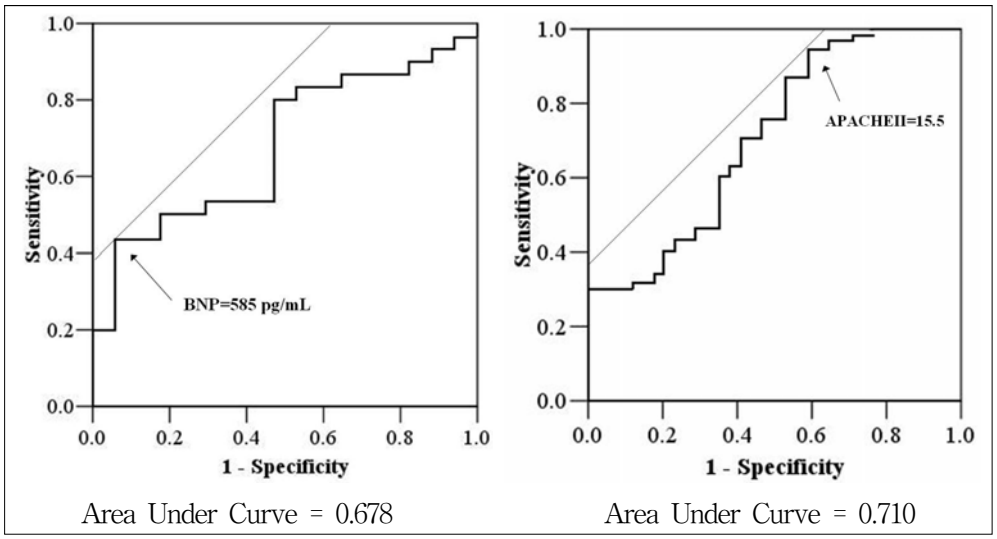

Figure 3. Receiver operating characteristic curve for BNP (left) APACHE II score (right) for the prediction of mortality. BNP: B-type natriuretic peptide; APACHE: Acute Physiology and Chronic Health Evaluation

Receiver operating characteristic (ROC) curve for the prediction of mortality

With the use of the threshold value for BNP of 585 pg/mL, the sensitivity for the prediction of mortality was 43%, with specificity of 94%, and area under the curve (AUC) of 0.678. The threshold value for APACHE II of 15.5 showed sensitivity of 87%, specificity of 47%, and AUC of 0.710 (Figure 3). In order to combine these two factors, we used log-transformed BNP values. 'APACHE II + 11×logBNP' showed the best result of AUC (0.747). Using the threshold value for 46.14, sensitivity was 63%, and specificity was 82% (Figure 4).

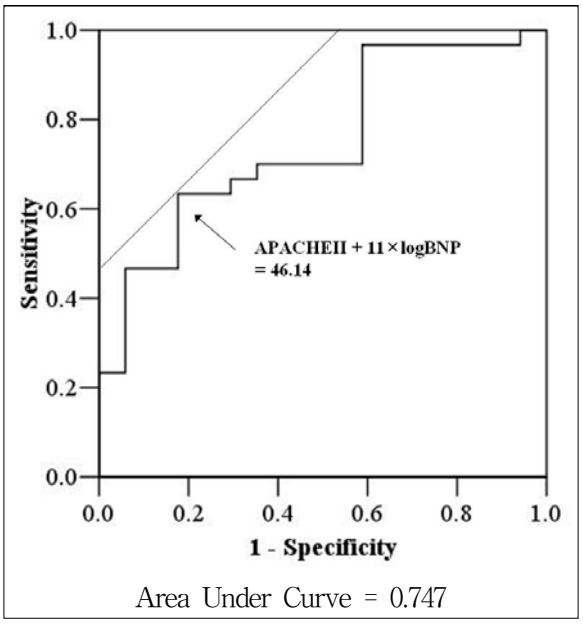

Figure 4. Receiver operating characteristic curve for 'APACHE II score + 11×log BNP' for the prediction of mortality.
BNP: B-type natriuretic peptide; APACHE: Acute Physiology and Chronic Health Evaluation

Sensitivity, specificity, PPV, NPV, AUC for BNP, APACHE II, and APACHE II + 11×logBNP are given in Table 5.

DISCUSSION

BNP can be elevated not only in CHF patients but also other critically ill patients[12,19]. Little is known in ARDS patients. Maeder and colleagues[10] reported one case of ARDS patient who showed marked elevation of BNP in spite of normal ejection fraction. Although there are some articles about BNP in respiratory failure patients[13,14], none of them were about only ARDS patients. We wanted to evaluate the relationship between BNP and mortality in ARDS patients, and also to exclude the effect of LV dysfunction on BNP. So, we enrolled patients who met the diagnostic criteria of ARDS, and ruled out any patients who had less than 50% of ejection fraction and/or any features of diastolic dysfunction. This can explain the relatively small number of patients in this study in spite of long study period.

BNP concentrations among those who died were higher than those who survived in shock patients[12]. Although APACHE II score is well known predictor of mortality in critically ill patients, there was no significant difference in APACHE II score between two groups in that study. In a Jefic D et al's study, mean BNP concentrations did not differ between the survivors and nonsurvivors in respiratory failure patients, and mean APACHE II scores were higher in nonsurvivors than in survivors[13]. In our study, not only BNP concentrations but also APACHE II scores are elevated significantly in patients who died. Our study is unique in that we enrolled only ARDS patients and ruled out LV dysfunction patients. This may be the reason of the different result compared to previous two similar studies. What we tried to show was BNP could be elevated in ARDS patients without the effect of LV dysfunction, and this elevation could be related to the mortality. We clearly showed that BNP

Table 5. Sensitivity, specificity, PPV, NPV, AUC for BNP, APACHE II, and APACHE II + 11×logBNP.

	Sensitivity	Specificity	PPV	NPV	AUC	p value
BNP≥585pg/dL	0.433	0.941	0.929	0.485	0.678	0.044*
APACHE II≥15.5	0.867	0.471	0.743	0.667	0.710	0.018*
APACHE II+11×logBNP ≥46.16	0.633	0.824	0.864	0.560	0.747	0.005†

PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; BNP: B-type natriuretic peptide; APACHE: Acute Physiology and Chronic Health Evaluation

concentrations and APACHE II scores were elevated significantly in nonsurvivors. BNP is useful biomarkers for the diagnosis of HF. However, BNP might be raised to different degrees in critical illness and various pulmonary diseases. In these situations, BNP may also serve as markers of severity and prognosis[18]. ARDS is one of these diseases, and we showed BNP > 585 pg/mL has a high specificity for the prediction of mortality.

APACHE II score is well known predictor of mortality in critical illness patients. BNP also seems to be the predictor of mortality. APACHE II score and BNP were not correlated significantly in critically ill patients[19]. In our study, the result was also same. We hypothesized that BNP could reflect certain conditions which APACHE II score couldn't cover. So, we combined there two markers hoping they could produce synergistic result in predicting mortality. BNP concentrations showed wide variation compared to APCHE II score, so log BNP was used to correct this problem. The concept of log BNP was adapted from previous published study[12]. Although there was no reference in combination of these two scores, we could prove 'APACHE II + 11×logBNP' was better than BNP or APACHE II in predicting mortality.

It is well known that the BNP is elevated in patients with low ejection fraction. However, in our study, there was no correlation between BNP concentration and EF. This may be due to the exclusion of patients who showed low ejection fraction. This result can tell we effectively eliminated the effect of LV dysfunction on BNP in our study, and we could examine more pure effect of ARDS on BNP concentration.

Sepsis, renal failure, pulmonary hypertension, right ventricular dysfunction, high PEEP, and shock state can be the cause of raised plasma BNP levels[18]. In ARDS patients, these conditions may coexist commonly. This may explain the reason of elevated level of BNP in ARDS. The high mortality rate in patients with high BNP levels may reflect these conditions. However, in our study, only sepsis patients showed just increased percentage of BNP elevation. We are not sure the elevation of BNP is due to sepsis in our study. No other medical conditions affected significantly the level of BNP. BNP concentration was also seemed not to be affected by the intubated state. Maybe this is because the number of enrolled patients was small, and/or there were another factors that we don't know which can elevate BNP levels. Recently, Karmpaliotis et al published similar result as ours[20]. BNP appears useful in excluding cardiogenic pulmonary edema, but some ARDS patients showed elevation of BNP in the absence of CHF. Among those patients, high BNP concentration was associated with mortality. Unfortunately, they also could not explain the pathogenesis of this result.

The limitation of our study is the small number of patients. A second limitation is that we only measured a single BNP concentration at the time of enrollment. As BNP is known to fluctuate, serial measurement of BNP may be more useful than single. Another limitation is that we did not measure N-terminal pro BNP (NT-pro BNP) which is also well known useful marker for the diagnosis of heart failure.

Our results are useful as they reflect information of only ARDS patients. All enrolled patients were compatible with the diagnostic criteria of ARDS. They are also unique in that they had normal ejection fraction. We showed that BNP and APACHE II score could predict mortality. When we combined these two factors, we could get better results. Further study about BNP in ARDS patients should be done.

SUMMARY

Background

B-type natriuretic peptide (BNP) has been shown to be strong mortality predictors in a wide variety of cardiovascular syndromes. Little is known about BNP in patients with acute respiratory distress syndrome (ARDS). We studied whether BNP can predict mortality in patients with ARDS.

Method

Echocardiographic study was done to all patients with ARDS, and we excluded patient with low ejection fraction (less than 50%) or showing any features of diastolic dysfunction. 47 patients were enrolled between December, 2003 and February, 2006. Parameters including BNP were obtained within 24h hours at the time of enrollment.

Result

Mean BNP concentrations and APACHE II scores differed between the survivors and nonsurvivors (BNP, 219.5 ± 57.7 pg/mL vs 492.3± 88.8 pg/mL; p=0.013, APACHE II score, 17.4 ± 1.6 vs 23.1 ± 1.3, p=0.009, respectively). With the use of the threshold value for BNP of 585 pg/mL, the specificity for the prediction of mortality was 94%. The threshold value for APACHE II of 15.5 showed sensitivity of 87%. 'APACHE II + 11×logBNP' showed sensitivity 63%, and specificity 82%, using threshold value for 46.14.

Conclusion

BNP concentrations and APCHE II scores were more elevated in nonsurvivors than survivors in patients with ARDS who have normal ejection fraction. BNP can predict mortality. Further study should be done.

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