# Clinical usefulness of N-terminal pro-brain natriuretic peptide levels in patients with acute lung injury/acute respiratory distress syndrome concomitant with septic shock

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# Clinical usefulness of N-terminal pro-brain natriuretic peptide levels in patients with acute lung injury/acute respiratory distress syndrome concomitant with septic shock

Directed by Professor **Joon Chang**

The Master's Thesis submitted to the Department of Medicine
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This certifies that the Master's Thesis of

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## ABSTRACT

Clinical usefulness of N-terminal pro-brain natriuretic peptide levels in patients with acute lung injury/acute respiratory distress syndrome concomitant with septic shock

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(Directed by Professor **Joon Chang**)

***Objective:*** To investigate the relationship between dynamic changes in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and clinical course/multiple organ failure in patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) accompanied by septic shock.

***Design:*** Prospective observational study.

***Setting:*** Intensive care unit.

***Patients:*** Forty nine patients who fulfilled American-European Consensus Conference definition for ALI/ARDS accompanied by septic shock.

***Interventions:*** None.

***Measurements and Main Results:*** Plasma NT-proBNP level was measured and SOFA score was calculated at days 0 (admission day), 1, 3, and 7. A 100% increase of NT-proBNP or more (NT-proBNP ratio $\geq$ 2.0) or a 50% decrease or more (NT-proBNP ratio $\leq$ 0.5) from the value of day 0 were considered significant change. The median NT-proBNP level was 3,594 pg/mL (interquartile range of 1,027~11,323

pg/mL). In a mixed model analysis, Time, and Group * Time effects were significant ($p = 0.027$ for survivors vs. non-survivors). Compared with survivors, non-survivors showed a significant increase in NT-proBNP levels after day 0 (within-group analysis). There was a significant increase in mortality and delta Sequential Organ Failure Assessment (ΔSOFA, change in SOFA from day 0) associated with an increasing NT-proBNP ratio at day 3 and day 7 ($p < 0.05$). NT-proBNP ratio correlated with ΔSOFA even after adjusting for age, sex, ejection fraction, and estimated glomerular filtration rate at each day ($p < 0.05$). NT-proBNP was comparable to SOFA in terms of 28 day mortality prediction by the receiver operating characteristic curve analysis.

***Conclusions:*** When ALI/ARDS patients are accompanied by septic shock, a trend of increasing NT-proBNP levels is a more reliable predictor of negative outcome than a high NT-proBNP level at a specific time point. For more accurate prognostication, NT-proBNP should be measured serially for more than two days after ICU admission. NT-proBNP may be used as a surrogate marker for SOFA score in evaluating multiple organ dysfunction.

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Key words : respiratory distress syndrome, acute lung injury, N-terminal pro-BNP, multiple organ failure

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## I. INTRODUCTION

The use of protective ventilator strategies that lower tidal volume and airway pressure has decreased the mortality of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), but it remains high [1, 2]. These conditions are characterized by increased alveolar-capillary permeability and loss of epithelial integrity, diffuse neutrophilic alveolar infiltrate, and accumulation of a protein-rich pulmonary edema, resulting in ventilation-perfusion mismatch and hypoxemic pulmonary vasoconstriction [3, 4], which can contribute to increased myocardial strain. In addition, accompanying septic shock [5], aggressive fluid resuscitation, use of vasopressor, and positive end-expiratory pressure (PEEP) can further affect myocardial function.

Because of the complex nature of ALI and ARDS, it is difficult for physicians to detect the true severity of the condition and predict the clinical course upon intensive care unit (ICU) admission, using only the American-European Consensus Conference (AECC) definitions for ALI/ARDS [6-8]. Recently, several biomarkers have been found to be meaningful in evaluating the severity and

prognosis of ALI/ARDS [9-11]. However, tests for these markers are not widely available at bedside.

Brain natriuretic peptide (BNP) is a cardiac neurohormone synthesized in ventricular cardiomyocyte. N-terminal pro-brain natriuretic peptide (NT-proBNP) is a biologically inactive form and cleaved out of the prohormone pro-brain natriuretic peptide (pro-BNP) by proteolytic enzymes before secretion [12]. In addition to promoting natriuresis and maintaining fluid and electrolyte homeostasis, BNP regulates cardiovascular hemodynamics, modulates myocardial hypertrophy and vascular remodeling, counteracts the renin-angiotensin-aldosterone axis, and inhibits thrombosis and systemic inflammation [12, 13]. A previous study showed that NT-proBNP levels were elevated among ARDS patients and that patients with levels above the cut-point value had significantly higher odds of mortality and higher organ dysfunction scores [14]. Besides myocardial depression, however, there are other factors that could lead to increased BNP secretion in ALI/ARDS. These include right ventricular strain associated with increased pulmonary vascular resistance [15], hypoxia [16], pro-inflammatory cytokines [17], and lung injury-induced BNP expression [18]. In addition, treatment-related factors, such as open lung ventilation with high PEEP, vasopressor use and goal-directed treatment strategy for septic shock [19] may also contribute to increased BNP levels. In this situation, it is unclear whether initial NT-proBNP levels can predict the outcome of patients who should improve after treatments. Therefore, it is important to investigate the utility of serially measured NT-proBNP levels in predicting the clinical course and degree of organ dysfunction in ALI/ARDS patients. Given the evidence that ALI/ARDS can increase myocardial stress and that increased NT-proBNP levels reflect an endocrine-cardiac response to stress [12], it can be hypothesized that a dynamic variation in NT-proBNP levels reflects the clinical course in patients with ALI/ARDS. The aim of this study was to investigate the relationship between dynamic changes in NT-proBNP levels and clinical course/multiple organ dysfunction in patients with ALI/ARDS.

## II. MATERIALS AND METHODS

### 1. Patients

This study was performed from June 2008 to April 2009 in the 30-bed ICU at Severance Hospital in Seoul. The protocol was approved by the Institutional Review Board and written informed consent was obtained from the patients or their next of kin. After a 6-hour stabilization period following initiation of mechanical ventilation, only those who fulfilled the AECC definitions for ALI/ARDS [6] were enrolled in the study. Septic shock was defined as sepsis with hypotension (arterial blood pressure <90 mmHg systolic, or 40 mmHg less than patient's normal blood pressure) for at least 1 hr despite adequate fluid resuscitation or as needed for vasopressors to maintain systolic blood pressure ≥90 mmHg or mean arterial pressure ≥70 mmHg. Sepsis was defined as systemic inflammatory response syndrome (SIRS) with proven or suspected microbial etiology. SIRS was defined as the presence of microbes or their toxins in blood or 2 or more of the following conditions (noninfectious etiology): (1) body temperature >38℃ or <36℃; (2) leukocytosis (>10,000/㎕) or leukopenia (<4,000/㎕) or >10% bands; (3) heart rate >90 beats/min; and (4) respiratory rate >24 breaths/min [20]. Exclusion criteria were age under 18 years, pregnancy, chronic obstructive/restrictive lung disease, intracranial disease, past history of lung resection, diffuse alveolar hemorrhage, bronchopleural fistula, pneumothorax, acute coronary syndrome or recent myocardial infarction, pulmonary thromboembolism or evidence of deep vein thrombosis, and end-stage renal disease requiring renal replacement therapy. Trans-thoracic echocardiography (Vivid-I; General Electric, Wisconsin, USA) was performed on every subject within 24 hours to evaluate cardiac function. Left ventricular systolic function was determined by measuring the ejection fraction (EF) according to the Simpson's method.

## 2. Respiratory and other usual critical care settings

All patients were placed in a semirecumbent position and given volume-controlled mechanical ventilator support (Galileo, software version GMP 03.43C, Hamilton Medical AG, Switzerland) with a tidal volume of 6 mL/kg predicted body weight. Respiratory rate, inspiratory to expiratory time ratio, and other respiratory settings were determined according to the low tidal volume strategy reported by the ARDSNet study of the National Heart, Lung, and Blood Institute [21]. Patients with septic shock were treated following the international guidelines for management of severe sepsis and septic shock [22]. All patients were sedated by continuous infusion of midazolam and alfentanil. The preferred vasopressor in the ICU was norepinephrine. Daily endotracheal aspiration was performed with a closed-suction system (Stericath 16 F, Portex, Keene, USA). To prevent ventilator-associated pneumonia, ventilator bundle series were applied to all patients, if not contra-indicated [23]. Once patients had been stabilized following fluid resuscitation and vasopressor treatment, the conservative fluid management strategy was applied [24].

## 3. Data collection

In all patients, baseline demographic data and clinical variables, including age, sex, primary diagnosis, cumulative amount of fluid balance, average amount of vasopressor given per hour on each day, duration of mechanical ventilation, length of stay (LOS) in the ICU, and outcome, were recorded. Acute Physiology and Chronic Health Evaluation (APACHE) II score, Simplified Acute Physiology Score (SAPS) II, Lung Injury Score (LIS), and Sequential Organ Failure Assessment (SOFA) score were calculated at days 0 (on admission), 1, 3, and 7, if data were available [25-27].

**4. NT-proBNP and routine blood sample collection**

Blood samples were taken using an indwelling arterial catheter. Plasma samples were taken from all patients at days 0, 1, 3, and 7. NT-proBNP levels were measured immediately using a commercially available immunoassay analyzer (NT-proBNP, Elecsys 2010, Roche Diagnostics, Mannheim, Germany). The measuring range of this assay extended from 5 to 35,000 pg/mL. Values higher than upper limit were obtained by diluting samples. The coefficient of variation for this assay was 2.6 ~ 3.2%.

**5. Statistical analysis**

Continuous variables were presented as mean ± standard deviation, or as median values and interquartile range when the assumption of normality was violated. Categorical variables were expressed as absolute and relative frequencies. Class comparisons were performed using the chi-square test or Fisher's exact test for binary variables, and the Kruskal-Wallis test for continuous variables, as appropriate.

Group and Time * Group effects were assessed by mixed model analysis. NT-proBNP values were log-transformed, to assume a normal distribution. Group, Time, and interaction between Group and Time were all regarded as fixed effects, and the covariance pattern of the repeated measurements was regarded as unstructured. The covariance parameter was estimated using the restricted maximum likelihood method (REML).

For all patients, mortality and delta SOFA (ΔSOFA, change in SOFA score from day 0 to later days) were evaluated in reference to NT-proBNP ratio (NT-proBNP value on the later days over the value of day 0). Considering intra-individual variations in NT-proBNP concentration [28] as well as various confounding factors affecting NT-proBNP levels [29], a 100% increase of NT-proBNP or more (NT-proBNP ratio ≥ 2.0, Increase group) or a 50% decrease or more (NT-proBNP ratio ≤ 0.5,

Decrease group) from the value of day 0 were considered significant. Patients with NT-proBNP ratio between 0.5 to 2.0 were classified into No change group. The correlation between NT-proBNP ratio and mortality was evaluated using the Cochrane-Armitage-trend test. The distribution of ΔSOFA among groups was compared using the Kruskal–Wallis test, followed by the Wilcoxon rank-sum test with the Bonferroni correction applied for multiple comparisons (the Wilcoxon rank-sum test was used at day 1 because of the absence of a decrease group).

The relationship between NT-proBNP level and APACHE II, SAPS II, SOFA score, each component of SOFA score, and ΔSOFA was tested by univariate analysis using the Spearman correlation method. If a significant relationship was found, the relationship was further evaluated by multiple regression analysis. Variables that were not significant in univariate analysis but had potential clinical importance and factors known to affect NT-proBNP level were introduced as covariates in a stepwise linear regression model. To compare the predictive power of the NT-proBNP and SOFA score, the area under the receiver operating characteristic curve (AUC) was calculated. Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Incorporated, Cary, NC). A p value of less than 0.05 was considered statistically significant.

## III. RESULTS

### 1. Baseline characteristics

A total of 49 patients were enrolled in this study. Forty-six patients (94%) had pulmonary ALI/ARDS. Table 1 shows baseline characteristics of the study population. The median value of NT-proBNP concentration at day 0 was 3,594 pg/mL with an interquartile range of 1,027~11,323 pg/mL.

**Table 1**. Baseline characteristics of the patients

| Variables | Data (n = 49) |
|---|---|
| Age | 64 ± 15 |
| Sex, male | 28 (57%) |
| $PaO_2/FiO_2$ initial | 145.2 ± 55.1 |
| $PaO_2/FiO_2$ after 24 hrs | 187.5 ± 90.1 |
| LIS | 12 ± 2 |
| APACHE II | 22 ± 6 |
| SAPS II | 48 ± 11 |
| SOFA | 8 ± 3 |
| Septic shock | 48 (98%) |
| ICU LOS (days) | 17 ± 17 |
| 28-day mortality | 32 (65%) |
| Ejection fraction (%) | 64 ± 8 |
| Fluid balance (mL) | 2,645 ± 2,203 |
| Norepinephrine (μg/kg/min) | 0.3 ± 0.4 |
| Renal dysfunction | 19 (39%) |
| NT-proBNP (pg/mL) | |
| Median | 3,594 |
| Interquartile range | 1,027-11,323 |

ARDS, acute respiratory distress syndrome; ALI, acute lung injury; ARF, acute respiratory failure; $PaO_2/FiO_2$ initial, $PaO_2/FiO_2$ ratio on ICU admission; $PaO_2/FiO_2$ after 24 hrs, $PaO_2/FiO_2$ ratio after 24 hrs of mechanical ventilation; LIS, lung injury score; APACHE II, Acute Physiology and Chronic Health Evaluation; SAPS II, Simplified Acute Physiologic Score II; SOFA, Sequential Organ Failure Assessment; ICU LOS, length of stay in intensive care unit; Fluid balance, sum of total fluid intake and output during first 24 hours in the intensive care unit; norepinephrine, average amount of norepinephrine infusion per hour during first 24 hours in the intensive care unit; Renal dysfunction, frequency of patients with estimated glomerular filtration rate < 60 mL/min/1.73 $m^2$; NT-proBNP, N-terminal probrain natriuretic peptide at intensive care unit admission; NS, nonsignificant.

Binary variables were compared using the chi-square test or Fisher's exact test; continuous variables were compared using Kruskal-Wallis test, as appropriate. Unless otherwise noted, data are presented as mean ± SD or absolute (relative) frequencies.

**2. Comparison of the dynamic variations of NT-proBNP levels within and between groups**

Figure 1 shows the change in NT-proBNP levels with time for each group. Group and Time * Group effects were statistically significant between survivors and non-survivors ($p = 0.027$). Compared to survivors, non-survivors showed a significant increase in NT-proBNP levels after day 0 (within-group analysis, $p < 0.05$) and even larger increase from initial levels after day 3 (between-group analysis, $p < 0.05$) (Table 2).

**Figure 1**. Time course of N-terminal probrain natriuretic peptide levels in survivors and non-survivors.

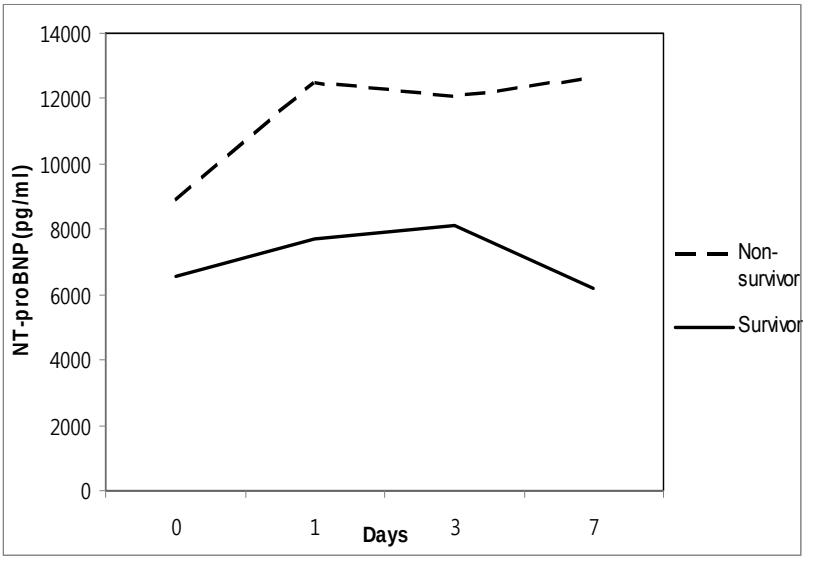



**Table 2.** Mixed model comparison of the dynamic variations of N-terminal probrain natriuretic peptide (NT-proBNP) levels within and between groups

| | Day 0 | Day 1 | Day 3 | Day 7 |
|---|---|---|---|---|
| Comparison of log NT-proBNP levels between groups | | | | |
| Survivors vs. Non-survivors | 0.19 (-0.83, 1.22) | 0.37 (-0.68, 1.42) | 1.12 (0.15, 2.09) | 1.68 (0.82, 2.54)* |
| | | Day 1 – Day 0 | Day 3 – Day 0 | Day 7 – Day 0 |
| Comparison of the change in log NT-proBNP levels from day 0 within groups | | | | |
| Survivors | | 0.13 (-0.17, 0.43) | 0.00 (-0.68, 0.69) | -0.29 (-1.03, 0.46) |
| Non-survivors | | 0.31 (0.11, 0.5)* | 0.93 (0.45, 1.40)* | 1.20 (0.65, 1.75)† |
| Comparison of the change in log NT-proBNP levels from day 0 between groups | | | | |
| Survivors vs. Non-survivors | | 0.17 (-0.18, 0.53) | 0.93 (0.09, 1.76) | 1.49 (0.57, 2.41)* |

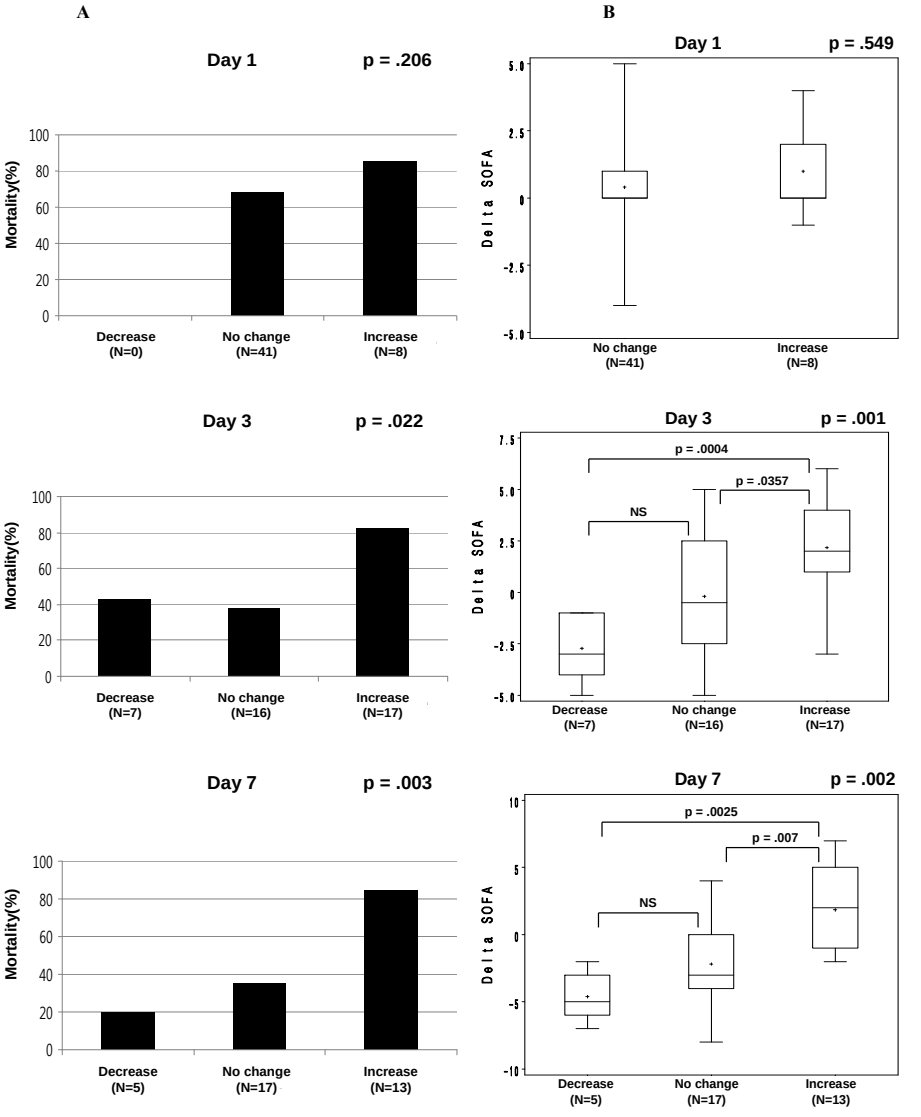
Data presented are median (25th, 75th percentile). NT-proBNP concentrations were log-transformed using the natural logarithm to the base e. Data were estimated from least square means by mixed model analysis. For multiple comparison of log NT-proBNP levels within and between groups from day 0, p values were adjusted by the

Bonferroni correction (*p < .05, †p <.001).

**3. Mortality and ΔSOFA in relation to NT-proBNP ratio**

There were no patients allocated to the decrease group on day 1. There was a significant trend toward increasing 28-day mortality associated with increasing NT-proBNP ratio at days 3 and 7 ($p < 0.05$) (Fig. 2A). When compared with No change group, only increase group showed statistically significant differences in ΔSOFA after day 3 ($p < 0.05$) (Fig. 2B).

**Figure 2**. Twenty-eight day mortality (A) and delta Sequential Organ Failure Assessment (ΔSOFA, the change in SOFA score from day 0 to later days) (B) in relation to N-terminal probrain natriuretic ratio (NT-proBNP value of the later days over the value of day 0). Decrease, No change, and Increase denote groups of patients with NT-proBNP ratios below 0.5, between 0.5 and 2.0, and above 2.0, respectively. There was no patient allocated to the Decrease group at day 1. The p-value stated in Figure A is for the Cochran-Armitage trend test. The p-value stated in Figure B is for post-hoc analysis by Wilcoxon rank sum test with the Bonferroni correction (adjusted p-value of $\leq 0.0167$ was considered statistically significant). The difference of delta SOFA between the Decrease group and the No change group was not significant (NS).




## 4. Relationship between NT-proBNP and SOFA

Among the severity scores, only the SOFA score was correlated with NT-proBNP level at ICU admission in univariate analysis (p = 0.265 with APACHE II, p = 0.132 with SAPS II, p = 0.0001 with SOFA; Spearman correlation coefficient = 0.517 for SOFA). Of the six components of SOFA subscores at day 0, platelet count

($p < 0.0001$), vasopressor dose ($p < 0.0001$), and creatinine level ($p = 0.0034$) were correlated with NT-proBNP level (correlation coefficients: -0.613, 0.608, and 0.411, respectively). This correlation remained significant at days 1 and 7 ($p = 0.0035$ and $p = 0.003$, respectively). In addition, the NT-proBNP ratio on days 1, 3, and 7 was correlated with the ΔSOFA of corresponding days in univariate analysis ($p = 0.016$, $p = 0.001$, and $p = 0.002$, respectively). This correlation remained significant at days 1, 3, and 7 by multiple linear regression analysis after adjustment for age, sex, EF, and eGFR ($p < .05$) (Table 3). Fluid balance and EF showed no correlation with NT-proBNP level.

**Table 3**. Association between N-terminal probrain natriuretic peptide (NT-proBNP) ratio and delta Sequential Organ Failure Assessment (ΔSOFA) by multiple regression analysis

| Time | Variables | Coefficient | Standard Error | P |
|---|---|---|---|---|
| Day 1 | NT-proBNP ratio | 0.467 | 0.152 | 0.004 |
| | Age | 0.011 | 0.017 | NS |
| | Sex | 0.293 | 0.505 | NS |
| | EF | 0.042 | 0.026 | NS |
| | eGFR | -0.002 | 0.006 | NS |
| Day 3 | NT-proBNP ratio | 0.286 | 0.074 | 0.001 |
| | Age | -0.023 | 0.029 | NS |
| | Sex | 0.543 | 0.869 | NS |
| | EF | 0.097 | 0.043 | 0.031 |
| | eGFR | -0.008 | 0.013 | NS |
| Day 7 | NT-proBNP ratio | 0.102 | 0.026 | 0.001 |
| | Age | 0.008 | 0.038 | NS |
| | Sex | 1.643 | 1.154 | NS |
| | EF | 0.048 | 0.054 | NS |
| | eGFR | -0.018 | 0.016 | NS |

ΔSOFA, the change in SOFA score from day 0 to designated day; NT-proBNP ratio, NT-proBNP value of designated day divided by the value of day 0. EF, ejection fraction; eGFR, estimated glomerular filtration rate; The multiple linear regression model was adjusted for age, sex, EF, and eGFR.

**5. Comparison of the predictive power of NT-proBNP and SOFA for 28-day mortality**

The receiver operating characteristic curves (ROC) of NT-proBNP levels used for 28-day mortality prediction are shown in Figure 3. The AUC had an increasing trend through day 3 that became significant at day 7 (p = .009). The AUC for NT-proBNP levels was comparable to that of SOFA scores for corresponding days (Table 4).

**Table 4**. Comparison of the area under the receiver operating characteristic curve (AUC) of N-terminal probrain natriuretic peptide (NT-proBNP) levels and Sequential Organ Failure Assessment (SOFA) scores for 28-day mortality at days 0, 1, 3, and 7

| Day | | AUC | 95% CI | Sensitivity | Specificity | PPV | NPV | p |
|---|---|---|---|---|---|---|---|---|
| Day 0 | NT-proBNP | 0.530 | 0.353-0.707 | 43% | 79% | 83% | 35% | NS |
| | SOFA | 0.635 | 0.466-0.804 | 40 % | 93% | 93% | 38% | |
| Day 1 | NT-proBNP | 0.558 | 0.386-0.730 | 44% | 79% | 83% | 37% | NS |
| | SOFA | 0.667 | 0.501-0.834 | 43% | 93% | 94% | 39% | |
| Day 3 | NT-proBNP | 0.648 | 0.456-0.841 | 77% | 57% | 77% | 57% | NS |
| | SOFA | 0.624 | 0.415-0.834 | 89% | 43% | 75% | 67% | |
| Day 7 | NT-proBNP | 0.769 | 0.588-0.950 | 76% | 79% | 84% | 69% | NS |
| | SOFA | 0.860 | 0.744-0.977 | 61% | 100% | 100% | 61% | |

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

## IV. DISCUSSION

This study showed that, in patients with ALI/ARDS: a) a trend of increasing NT-proBNP levels or high NT-proBNP ratio is better than high NT-proBNP levels at a particular time point for prediction of negative outcome in patients with ALI/ARDS accompanied by septic shock; b) For more accurate prognostication, NT-proBNP should be measured serially for more than two days after ICU admission; c) NT-proBNP level and ratio were correlated with SOFA score and ΔSOFA, respectively; and d) NT-proBNP may be used as a surrogate marker for SOFA score in predicting mortality.

A recent study by Bajwa et al. [14] reported that NT-proBNP levels can be used to predict outcomes of ARDS patients. However, single blood sampling within 48 hours of meeting ARDS criteria may be insufficient for determining the relationship between dynamic variation of NT-proBNP levels and clinical course of the disease. In addition, as has already been mentioned [15], the study time frame was over 6 years, and many critical care practices changed during that period, including fluid resuscitation and mechanical ventilation strategies. A considerable number of patients with ARDS have been reported to have concomitant myocardial depression [30], which is a major cause of natriuretic peptide secretion. Therefore, the authors sought to evaluate whether dynamic changes of NT-proBNP levels could reliably reflect the clinical course of the disease under uniform critical care practices.

In mixed model analysis, statistically significant differences were largely attributed to non-survivor groups rather than survivor groups. Consequently, a trend of increasing NT-proBNP levels was a more reliable predictor of negative outcome than a high NT-proBNP level at a specific time point. This pattern was also demonstrated by a significant trend toward increasing mortality and ΔSOFA with increasing NT-proBNP ratios. Clerico et al. [12] previously noted that the endocrine cardiac response to increasing stress may lead to elevated NT-proBNP levels and that this elevation should be considered as an activation index for the neuro-endocrine

system, rather than simply a marker of myocardial dysfunction. In accordance with Clerico et al., we suggest that non-survivors experienced incremental cardiac stress as reflected by incremental NT-proBNP levels. This incremental stress might have caused prolonged activation and exhaustion of the neuro-endocrine system, including the endocrine heart, thus contributing to hemodynamic instability and unfavorable outcomes. In the current study, NT-proBNP levels and ratios were correlated with SOFA score and ΔSOFA, respectively. Furthermore, NT-proBNP was comparable to SOFA in terms of mortality prediction, suggesting that NT-proBNP may have a clinical utility as a surrogate marker for SOFA.

These confounding factors may be one of the reasons for considerable overlap in the range of NT-proBNP levels between groups and wide distribution of cut-off values of NT-proBNP for predicting mortality from study to study [14, 31-35]. Among the six components of SOFA subscores, platelet count, vasopressor dose, and creatinine level were correlated with NT-proBNP values. This is consistent with results from another study performed on a non-cardiac, general ICU population [34]. It is conceivable that the threshold for sensing and responding to equivalent stress levels may be different from patient to patient. This individual variation could also be one of the reasons for the considerable overlap in the distribution of NT-proBNP levels between groups. To correct for this potential variability, we utilized NT-proBNP ratios instead of levels at a specific time point.

The appropriate frequency and timing of NT-proBNP measurement for prognostication purposes has not been determined. McLean et al. [36] concluded that, for patients with sepsis, neither the BNP levels from the first 3 days, nor daily changes in BNP levels, could be used as predictors for in-hospital mortality or length of stay. In contrast, Varpula et al. [31] noted that NT-proBNP levels measured on the third day in the ICU are an independent prognostic tool for mortality in severe sepsis. In another study by Post et al. [37], BNP concentration on day 5 could predict which patients would have unfavorable outcomes. Although the different etiologies and heterogenous population limit comparability, our study also showed that more than 2

days had been required before the differences in mortality rate and ΔSOFA between groups reached certain level of statistical significance. The AUC of NT-proBNP levels increased without statistical significance until day 3, again suggesting that more than 2 days after ICU admission may be required for prognostication. In our opinion, initial goal-directed treatments [19] contributed to the considerable elevation of NT-proBNP levels for the first few days after ICU admission. Thus, a certain time period may be required to cut out this "background noise" and evaluate the true meaning of elevated NT-proBNP levels with regard to the patient's condition.

The current study has several limitations. First or all, the population size was relatively small, and about 40% of the population was immunosuppressed, leading to a relatively high 28-day mortality rate. This could limit the generalizability of the current results. Second, we were unable to include all confounding variables that potentially influence NT-proBNP levels [38]. Specifically, the EF of each patient could not be measured serially. Thus, the presence of newly-developed myocardial dysfunction within 7 days could not be ruled out. However, we found that the EF did not correlate with NT-proBNP levels. Importantly, before estimating EF or other parameters, the definition of heart failure in ICU patients should be reconsidered. Neither normal cardiac index, nor left ventricular ejection fraction within the normal range as defined in healthy population, can exclude the presence of myocardial depression or heart failure in patients with ARDS or septic shock [39]. Moreover, continuous infusion of norepinephrine may influence ventricular systolic function by β-adrenergic stimulation thus increasing the cardiac index. Therefore, arbitrarily chosen cut-off values of cardiac index and ventricular EF may act as additional confounding factors in the evaluation of NT-proBNP levels. Third, about 40% of the population had renal dysfunction (defined as a eGFR < 60 mL/min/1.73m$^2$). Given that renal dysfunction is a major source of NT-proBNP elevation, clinicians should be cautious when interpreting NT-proBNP levels in patients with renal dysfunction [38]. However, as this condition was already reflected in both NT-proBNP levels and SOFA scores, it may not have altered our results.

## V. CONCLUSION

This study showed that, for patients with ALI/ARDS accompanied by septic shock, a trend toward increasing NT-proBNP levels is a more reliable predictor of negative outcome than a high level at specific time point. For more accurate prognostication, this biomarker should be measured serially for more than two days after ICU admission. Given the evidence that NT-proBNP level and ratio correlated with SOFA score and ΔSOFA, respectively, and that NT-proBNP was comparable to SOFA in terms of mortality prediction, our results suggest that NT-proBNP has a potential utility as a surrogate marker for SOFA.

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**ABSTRACT (IN KOREAN)**

# 패혈성 쇼크가 동반된 급성폐손상/급성호흡부전 환자들을 대상으로 한 N-terminal pro-brain natriuretic peptide 연속 측정의 임상적 유용성


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**목적:** 패혈성 쇼크가 동반된 급성폐손상 및 급성호흡곤란증후군 환자들을 대상으로 중환자실 입실 후 연속적으로 측정된 N-terminal pro-brain natriuretic peptide(NT-proBNP) 수치의 변화가 임상경과 및 다발성 장기부전을 어느 정도 반영하는지 확인하고자 하였다.

**대상 및 방법:** 2008 년 6 월부터 2009 년 4 월까지 세브란스병원 내과계 중환자실에 입실한 환자들 중 패혈성 쇼크가 동반된 급성폐손상 및 급성호흡곤란증후군 환자들을 전향적으로 모집하여 입실 당일, 1 일, 3 일, 7 일에 NT-proBNP 를 측정하였다. 입실 당일의 NT-proBNP 수치와 비교하여 100% 이상 증가하거나(NT-proBNP ratio ≥ 2.0), 50% 이상 감소하는 경우(NT-proBNP ratio ≤ 0.5)를 의미 있는 변화로 간주하였다.

**결과:** NT-proBNP 수치의 중앙값은 3,594 pg/mL (interquartile range 1,027~11,323 pg/mL)이었다. 혼합모델분석(mixed model analysis) 결과, 생존군 및 비생존군에서 시간 및 집단 * 시간의 효과를 고려한 NT-proBNP 의

변화는 통계적으로 의미있는 차이($p = 0.027$)를 보였으며, 집단 내 비교에서 비생존군은 생존군에 비해 입실 후 더 큰 증가를 보였다. 입실 후 3 일째와 7 일째를 기준으로 NT-proBNP ratio 가 증가한 군의 사망률 및 ΔSOFA (delta Sequential Organ failure Assessment)는 NT-proBNP ratio 가 감소하거나 변화가 없었던 군들에 비해 높았다($p < 0.05$). 나이, 성별, 심초음파 상 좌심실구출율, 사구체여과율로 보정을 한 상태에서 NT-proBNP ratio 는 ΔSOFA 와 입실 후 1 일, 3 일, 7 일째 모두 양의 부분상관관계를 보였다($p < 0.05$). receiver operating characteristic curve 를 이용한 28 일 사망의 예측력에 있어서 NT-proBNP 는 SOFA 체계와 통계적 차이를 보이지 않았다.

**결론:** 패혈성 쇼크가 동반된 급성폐손상 및 급성호흡곤란증후군 환자들을 대상으로 한 예후 예측에 있어서는 특정 시점에서의 증가된 NT-proBNP 수치보다는 NT-proBNP 의 증가추세가 더 신뢰할 수 있는 예측인자이었다. 예후예측을 목적으로 NT-proBNP 를 측정할 경우 중환자실 입실 후 2 일 이상 연속적으로 측정하는 것이 필요하였다. NT-proBNP 와 SOFA 의 28 일 사망에 대한 예측력은 차이가 없었다.

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핵심되는 말 : 급성호흡곤란증후군, 급성폐손상, N-terminal pro-BNP, 다발성 장기부전