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# Predicting cardiogenic pulmonary edema in heart failure patients by using an N-terminal pro-b-type natriuretic peptide (NT-pro BNP) -based score

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ABSTRACT

*Background:* Cardiogenic pulmonary edema (CPE) is a life-threatening emergency necessitating aggressive management. We conducted this study to test the hypothesis that a combination of N-terminal pro-b-type natriuretic peptide (NT-pro-BNP) and some relevant clinical factors may provide better predictability for CPE in heart failure (HF) patients.

*Methods:* This retrospective study enrolled adult HF patients hospitalized during January 2011 to December 2013. After determining the independent predictors for the occurrence of CPE, a novel NT-pro BNP-based diagnostic score for predicting CPE was established.

*Results:* A total of 269 patients (mean age, 74.5 ± 13.6 years; female, 53.9%) were enrolled, and categorized into CPE group ($n$ = 80, 29.7%) and non-CPE group ($n$ = 189, 70.3%). Several factors such as "Serum NT-pro-BNP level > 6980 mg/dl," "systemic blood pressure > 170 mm Hg," "heart rate > 120 bpm," "with rales in breathing sound," "with jugular vein engorgement," "with NYHA Fc III/IV," "with chronic lung disease" and "with angiotensin converting enzyme inhibitors/angiotensin receptor blocker" were found to be associated with the existence of CPE. A novel NT-pro BNP based scoring system containing these risk factors was proposed and proven excellent in predicting CPE.

*Conclusions:* The NT-pro-BNP scoring system could predict CPE in HF patients.

## 1. Introduction

Cardiogenic pulmonary edema (CPE), a complication occurring in 16% of hospitalized patients with heart failure (HF), [1,2] is a life-threatening emergency with high in-hospital mortality rate necessitating aggressive management [3,4]. The stepwise diagnostic interventions for patients with suspected HF are currently recommended as following: (1) Assessing the probability of HF using patients' medical histories, physical examinations, and electrocardiography (ECG), (2) Confirming the diagnosis for those with abnormal ECG findings using the B-type natriuretic peptide (BNP) or N-terminal pro-b-type natriuretic peptide (NT-pro-BNP) level along with other blood tests, (3) Comprehensive assessing for the associated complications, such as CPE, using chest radiography (CXR) and echocardiography in HF patients [5]. According to the recommendation, identification of CPE by CXR is the last step of working diagnosis. Additionally, differentiating CPE on CXR from other non-cardiogenic lung infiltrates or edema, such as pneumonia and acute respiratory distress syndrome (ARDS), is often challenging in the early stages of illness [4,6,7].

It is known that early differential diagnosis of CPE vs. ARDS is associated with an improved prognosis of HF patients [8]. However, the accuracy of distinguishing CPE from noncardiogenic dyspnea by emergency physicians was only 0.77, which was significantly lower than the accuracy of BNP-assisted diagnosis (0.84) [9]. Therefore,

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creating a reliable marker or diagnostic score for early identification of CPE is very important for the evaluation and management of HF patients.

BNP and NT-pro-BNP are peptides secreted by the heart in response to ventricle volume inflation [10]. They have been widely used as screening and diagnostic tools for HF [11–13]. They are also reliable biomarkers for recognizing CPE from other etiologies of dyspnea and for improving the judgment and management for acute dyspnea patients in the emergency department [14–17]. In our previous work, we demonstrated that a scoring system composed of NT-pro-BNP and nine risk factors performed better than NT-pro-BNP level alone in predicting in-hospital mortality among hospitalized HF patients [18]. We hypothesized that a combination of NT-pro-BNP and other relevant clinical factors might also provide better power for predicting CPE in HF patients, and therefore conducted this study trying to establish a novel NT-pro BNP-based scoring system to test the hypothesis.

## 2. Material and methods

### 2.1. Ethics, consent, and permissions

The Institutional Review Board of Saint Mary's Hospital Luodong reviewed and approved this study. The study was carried out with the approved protocols. Informed consents were waived since there was no breach of privacy or interference with therapeutic strategy making.

### 2.2. Study design and participants selection

This retrospective study was conducted using a HF cohort in a regional teaching hospital in Taiwan during the period January 1, 2011, to December 31, 2013. The details of patient selection and data gathering were described in our previous work [18]. Briefly, eligible participants were adult patients hospitalized due to HF confirmed by all the following criteria: (1) serum NT-pro BNP drawn at initial presentation which fulfilled the age-related cut-points for HF; (2) confirmation of HF by echocardiography during the hospitalization; (3) final diagnosis of HF (International Classification of Diseases-9 code, 428, 428.0, 428.1, and 428.9) at hospital discharge. The age-specific serum NT-pro BNP cut-points which had been proven to identify HF patients were as follows: (1) $>$ 1800 pg/ml in patients $>$ 75 y; (2) $>$ 900 pg/ml in patients aged 50–75 y; and (3) $>$ 450 pg/ml in patients $<$ 50 y [19].

The exclusion criteria included patients $<$ 18 y and patients with decompensated hepatic diseases with ascites and kidney failure necessitating dialysis. Patients with histories of severe chronic lung diseases (CLD) (i.e., forced expiratory volume in 1 s of $<$ 1 l) were also excluded because patients with poor lung function may suffer from severe chronic dyspnea with repeated acute dyspnea attacks, increasing the difficulty of distinguishing HF from severe CLD.

### 2.3. Measurements

The demographic data, comorbidities, etiologies of HF, drug history prior to the hospitalization, clinical variables at initial presentation and echocardiography reports during hospitalization, along with the outcomes variable such as length of stay (LOS) in hospital and intensive care unit (ICU), ventilation support, vasopressor prescription were all documented from medical records. The physical examination findings at the initial presentation were documented by physicians in the Emergency Department and rechecked by a cardiologist in wards or intensive care units. In the case that one patient had more than one hospitalization, only the first hospitalization was included in the current study.

CPE was defined by (1) increasing white shadow over both lung fields in CXR confirmed by a radiologist and (2) final diagnosis of pulmonary edema (ICD-9 518.4) made by a cardiologist at hospital discharge. The additional checks were to ensure the accurate diagnosis of CPE since CPE can be difficult to differentiate from initial stages of lung infection by CXR, but could be confirmed by the response to appropriate treatment.

### 2.4. Statistical analysis

Statistical analyses were undertaken using Scientific Package for Social Science and R 3.3.2 (R Foundation for Statistical Computing) software. Sigma Plot software ver 12.5 was applied to draw plots. In all statistical analyses, a $p \leqq 0.05$ was considered statistically significant. Continuous variables were reported as the mean ± SD and compared using an independent *t*-test, whereas categorical variables were expressed as case number (percentage) and compared using chi-square test.

The variables of statistical significance in the 2-group comparisons were chosen for multivariate analysis using the conditional forward stepwise model of the logistic regression method, to investigate their regression coefficient (B), odds ratio (OR), and *p*-value for CPE. The elimination criterion for the multivariate analysis was set at $p > 0.05$. Before being put into the multivariate analysis, the continuous variables were transformed into categorical variables by using their best cut points for predicting CPE by generalized additive models (GAM). The internal validity of current analysis was verified by a bootstrap simulation (* 2000) [20]. After that, the resampling procedures were undertaken and applied to an appropriate joint distribution, to estimate covariance matrices, make bias corrections, and construct confidence intervals (CIs).

Subsequently, a NT-pro BNP-based scoring formula was generated by the regression coefficient which was identified in the multivariate model. The scores of the individual variables were composed of the arithmetic sum of B coefficients after each numerical rounding derived from logistic regression analysis. Hosmer and Lemeshow Goodness-of-Fit test were used for calibration of the model [21]. Collinearity diagnosis with tolerance value and variance inflation factor was used to evaluate the correlation among the independent risk factors of CPE. Receiver operating characteristic (ROC) curve with an area under the curve (AUC) was used to compare the predictive abilities for CPE of the serum NT-pro-BNP level and the NT-pro BNP-based scores. The sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) were also calculated.

Finally, this score was categorized into three groups according to the risks (low, medium, and high risk) of CPE. Pearson's correlation test was applied to evaluate the correlation between the individual variables composed in the NT-pro BNP-based score and patient outcomes which were significantly different between CPE and non-CPE groups. The variables of significant correlation with patient outcomes in Pearson's correlation test were further selected for multivariate analysis using the conditional forward stepwise model of the logistic regression method or linear regression method, to investigate their regression coefficient, OR and *p*-value. The elimination criterion for the multivariate analysis was set at $p > 0.05$.

The calculated power of logistic regression method in our study using the G-Power was 1.00 when setting $\alpha$ as 0.05 and OR as 2.74. The OR of 2.74 was estimated from simple logistic regression which evaluated the association of CPE and NT-pro-BNP levels in categorical form (categorized by its best cut point calculated by GAM).

## 3. Results

During the study period, 1276 patients were screened, and 1007 patients were excluded (990 patients due to lack of final diagnosis of HF at discharge, age $<$ 18 y, and possession of severe CLD, decompensated hepatic diseases with ascites, or renal failure requiring renal replacement therapy. There were also 17 patients excluded due to a lack of echocardiography examinations) during the selection process. In