The role of brain natriuretic peptide in predicting renal outcome and fluid management in critically ill patients

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KEYWORDS
acute kidney injury; brain natriuretic peptide; fluid therapy; intensive care unit; mortality

Background/Purpose: Fluid overload is associated with acute kidney injury (AKI) and mortality. There is no convenient precise method to guide fluid therapy in critically ill patients. We aimed to investigate whether brain natriuretic peptide (BNP) can predict the renal outcome and mortality of critically ill patients and be used to guide fluid management.

Methods: This prospective observational study included patients who were admitted to the intensive care unit (ICU). Patients with underlying heart disease and heart dysfunction were excluded. Plasma BNP levels were obtained on admission (D0), at 24 hours (D1), and at 48 hours (D2). The primary outcome was AKI development during the ICU stay and recovery of AKI at ICU discharge. The secondary outcome was in-ICU mortality.

Results: One hundred and sixty-three patients were enrolled for analysis. The delta-BNP level within the initial 24 hours after ICU admission rather than fluid accumulation was significantly correlated with delta-central venous pressure levels ($r = 0.219, p = 0.010$). Delta-Brain natriuretic peptide levels of $< 81.8\%$ within the initial 24 hours was an independent predictor of better renal outcome (i.e., no AKI or AKI with recovery). The increment in the BNP level from D0 to D1 was also a significant risk factor of mortality. In the a priori subgroup analysis for...
Introduction

Acute kidney injury (AKI) is a common complication of patients in an intensive care unit (ICU), and it is an independent predictor of outcome. Many investigators have reported that fluid overload results in poor renal outcomes and higher mortality in critically ill patients with AKI. Patients in shock need intensive hydration to restore hemodynamic stability and renal blood flow; however, too much fluid damages internal organs, including the kidney. Therefore, to prevent AKI and to enhance recovery, a fast, simple, and cost-effective method is needed that can predict renal outcome and precisely guide fluid therapy, which involves initial volume resuscitation, subsequent serial fluid status assessment for fluid balance, and appropriate timing of fluid removal. However, various traditional methods used to guide fluid therapy are invasive and inconvenient.

Brain natriuretic peptide (BNP) is a biomarker that can be easily obtained. It is a plasma neurohormone produced primarily by ventricular myocardiocytes in response to myocardial stretching and volume overload. Brain natriuretic peptide has been used to guide fluid management in patients with heart failure and in patients on hemodialysis. Furthermore, many investigators have reported an association between the absolute BNP level and mortality in critically ill patients. Therefore, our hypothesis was that the BNP level could also predict renal outcome and it has the potential to be a convenient cost-effective marker for fluid management in critically ill patients. The first aim of our study was to specify the association between the delta-BNP level and patient outcomes (i.e., AKI occurrence, recovery, and mortality). The second aim was to evaluate which range of delta-BNP levels is suitable for critical patients to avoid poor renal outcome induced by fluid overload.

Methods

Study population and protocol

This prospective observational study was approved by the Institutional Review Board of the National Taiwan University Hospital (Taipei, Taiwan; approval number 201111012RIB). All participants or their legal representatives provided written informed consent. This study was performed in compliance with the declaration of Helsinki.

We included 163 patients in the final analysis, after consecutively selecting patients who were older than 18 years and admitted to the ICU of a university hospital between April 2012 and June 2014 (Figure 1). To avoid the effects of other causes of chronic or severe heart dysfunction on the BNP level, the study investigators excluded patients with chronic heart disease (based on chart reviews), with an abnormal echocardiogram on admission (i.e., systolic dysfunction: left ventricular ejection fraction < 55%; diastolic dysfunction: E wave/A wave ratio < 0.75 or > 1.5), acute coronary syndrome, acute myocardial infarction, acute pulmonary embolism, status post cardiopulmonary resuscitation, cor pulmonale, and respiratory failure with high positive end-expiratory pressure (> 10 cmH₂O). Plasma BNP levels were obtained on ICU admission [i.e., Day 0 (D0)], at 24 hours [i.e., Day 1 (D1)], and at 48 hours [i.e., Day 2 (D2)]. Plasma BNP samples were separated from the cells immediately, stored at 4°C, and measured within 4 hours using an automated microparticle enzyme immunoassay (AxSYM; Abbott, Park, Illinois, USA). The intensive care specialists were blinded to the BNP levels.

The primary outcome was AKI development during the ICU stay and recovery of AKI at ICU discharge. The secondary outcome was in-ICU mortality. On ICU admission or during the ICU stay, AKI was diagnosed when a patient had an incremental increase in serum creatinine of > 0.3 mg/dL within 48 hours or an increase of at least 50% from the baseline within 7 days or a urine output of < 0.5 mL/kg/h for > 6 hours. Acute kidney injury recovery was defined as a decrease in the serum creatinine level at ICU discharge by at least 50% from the peak value. The patients were divided into the group with better renal outcome (i.e., no AKI or AKI with recovery during the ICU stay) and the group with worse renal outcome (i.e., AKI without recovery during the ICU stay). The study investigators also classified the causes of the ICU admission and AKI.

Data collection

All data were prospectively collected. Demographic data, comorbid diseases, severity scores such as the Glasgow Coma Scale score, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and the Sequential Organ Failure Assessment (SOFA) score were determined at ICU admission. Blood chemistry and clinical parameters were measured before and after the ICU stay. The patients’ body weight, and fluid intake and output were obtained daily during the ICU stay. Fluid accumulation was calculated by the following formula:

$$\sum_{\text{daily}} \left[ \text{fluid intake (mL)} - \text{total output (mL)} \right]. \quad (1)$$

Chronic kidney disease is defined as an abnormality in the kidney structure or function that is present for > 3 months.
Statistical analysis

The statistical analysis was performed using R 3.1.0 software (R Foundation for Statistical Computing, Vienna, Austria). For statistical testing, two-sided p values of ≤ 0.05 were considered statistically significant. The distributional properties of continuous variables were expressed by the mean ± the standard deviation. Categorical variables were represented by the frequency and percentage. In univariate analysis, the two-sample t test, Wilcoxon rank-sum test (or Mann–Whitney U test), and the Chi-square test were used to examine the differences between the better and worse renal outcome groups in the distributions of the continuous variables and categorical variables. Multivariate analysis was then conducted by fitting logistic regression models to estimate the effect of predictors on the binary outcomes.

Basic model-fitting techniques for variable selection, goodness-of-fit (GOF) assessment, and regression diagnostics and remedies were used in the regression analyses to ensure analytical quality. In particular, the stepwise variable selection procedure (with iterations between the forward and backward steps) was applied to obtain the best candidate final regression model. All univariate significant and nonsignificant relevant covariates were included in the variable list (Table 1). The significance levels for entry and staying were set to 0.15 (or larger) to be conservative. With the aid of substantive knowledge, the best candidate final regression model was then identified manually by dropping in covariates with p > 0.05 one at a time until all regression coefficients were significantly different from 0.

The estimated area under the receiver operating characteristic curve (also called the c statistic), adjusted generalized $R^2$, and the Hosmer–Lemeshow GOF test were examined to assess the GOF of the fitted logistic regression model. An adjusted generalized $R^2$ of ≥ 0.30 indicated an acceptable fit. A c statistic value of ≥ 0.7 also indicated an acceptable level of discrimination power. Larger p values of the Hosmer–Lemeshow GOF test indicated better fits of the logistic regression model.

We also used generalized additive models to detect nonlinear effects of continuous covariates and to identify appropriate cutoff points for making continuous covariates discrete, if necessary, during the stepwise variable selection procedure. We performed a priori subgroup analysis for patients with sepsis because fluid management of septic patients is critical. Based on the results of logistic regression modeling of AKI recovery and mortality, we chose two fluid status parameters to test their interaction with sepsis in the regression analysis: (1) the percent change in BNP level from D0 to D1 and (2) fluid accumulation during the ICU stay.

Results

Patients’ characteristics

Most patients were admitted to the ICU because of septic shock and respiratory failure (Table S1). Sepsis was the
major cause of all AKI. Acute kidney injury caused by hypovolemic shock was more frequent in the AKI with recovery group.

We enrolled 163 patients. Among these patients, the no AKI or AKI with recovery group accounted for 84.0% of patients (Table 1). Compared to the no AKI or AKI with recovery group, the AKI without recovery group had a higher malignancy rate (p < 0.001), higher heart rate (p = 0.021), higher serum creatinine level on ICU admission (p = 0.023), lower white blood cell count (WBC; p = 0.011), higher

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 163)</th>
<th>AKI without recovery (n = 26)</th>
<th>No AKI (n = 38) or AKI with recovery (n = 99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>67.5 (± 13.4)</td>
<td>71.4 (± 12.0)</td>
<td>67.0 (± 13.5)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>106 (65.0)</td>
<td>16 (61.5)</td>
<td>90 (65.7)</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dL)</td>
<td>1.04 (± 0.68)</td>
<td>1.27 (± 1.02)</td>
<td>1.01 (± 0.61)</td>
</tr>
<tr>
<td>Comorbid disease (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>68 (41.7)</td>
<td>9 (34.6)</td>
<td>59 (43.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>83 (50.9)</td>
<td>14 (53.8)</td>
<td>70 (51.1)</td>
</tr>
<tr>
<td>CKD</td>
<td>19 (11.7)</td>
<td>3 (11.5)</td>
<td>16 (11.7)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>22 (13.5)</td>
<td>5 (19.2)</td>
<td>17 (12.4)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>20 (12.3)</td>
<td>3 (11.5)</td>
<td>17 (12.4)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>11 (6.7)</td>
<td>5 (19.2)</td>
<td>6 (4.4)</td>
</tr>
<tr>
<td>CVA</td>
<td>14 (8.6)</td>
<td>2 (7.7)</td>
<td>12 (8.7)</td>
</tr>
<tr>
<td>Clinical parameters on ICU admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>81.1 (± 19.3)</td>
<td>88.2 (± 23.8)</td>
<td>80.0 (± 18.5)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>36.4 (± 1.5)</td>
<td>36.5 (± 1.4)</td>
<td>36.4 (± 1.6)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>107.2 (± 21.6)</td>
<td>117.3 (± 19.7)</td>
<td>105.8 (± 21.6)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>2.3 (± 2.0)</td>
<td>3.3 (± 2.6)</td>
<td>2.2 (± 1.8)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.1 (± 2.5)</td>
<td>10.7 (± 2.5)</td>
<td>11.2 (± 2.5)</td>
</tr>
<tr>
<td>WBC (/μL)</td>
<td>14786.0 (± 9323.8)</td>
<td>10749.5 (± 9247.2)</td>
<td>15354.1 (± 9227.0)</td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>134.6 (± 8.4)</td>
<td>135.5 (± 10.4)</td>
<td>134.5 (± 8.2)</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>4.0 (± 0.9)</td>
<td>4.0 (± 0.7)</td>
<td>4.0 (± 0.9)</td>
</tr>
<tr>
<td>Serum lactate (mmol/L)</td>
<td>1.1 (± 0.8)</td>
<td>1.4 (± 0.6)</td>
<td>1.1 (± 0.8)</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.0 (± 0.6)</td>
<td>3.0 (± 0.6)</td>
<td>3.0 (± 0.6)</td>
</tr>
<tr>
<td>BNP D0 (pg/mL)</td>
<td>749.9 (± 959.9)</td>
<td>963.6 (± 999.4)</td>
<td>719.8 (± 955.2)</td>
</tr>
<tr>
<td>BW D0 (kg)</td>
<td>57.8 (± 13.3)</td>
<td>60.6 (± 13.8)</td>
<td>57.4 (± 13.2)</td>
</tr>
<tr>
<td>CVP level</td>
<td>10.3 (± 6.1)</td>
<td>10.7 (± 4.6)</td>
<td>10.2 (± 6.3)</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>21.2 (± 8.6)</td>
<td>27.4 (± 7.2)</td>
<td>20.3 (± 8.3)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>8.0 (± 3.5)</td>
<td>9.9 (± 2.7)</td>
<td>7.7 (± 3.5)</td>
</tr>
<tr>
<td>GCS score</td>
<td>11.6 (± 3.6)</td>
<td>11.5 (± 2.9)</td>
<td>11.6 (± 2.9)</td>
</tr>
</tbody>
</table>

Data are presented as the n (%) or mean (± standard deviation). AKI = acute kidney injury; APACHE II = Acute Physiology and Chronic Health Evaluation II; BNP = brain natriuretic peptide; BW = body weight; CKD = chronic kidney disease; GCS = Glasgow Coma Scale; CVA = cerebrovascular accident; CVP = central venous pressure; ICU = intensive care unit; SOFA = Sequential Organ Failure Assessment; WBC = white blood cell.
serum lactate level \( (p = 0.014) \), and greater fluid accumulation during their ICU stay \( (p < 0.001) \). The plasma BNP levels on D1 \( (p < 0.001) \) and D2 \( (p < 0.001) \), APACHE II score \( (p < 0.001) \), SOFA score \( (p < 0.001) \), and mortality \( (p < 0.001) \) were also higher in the AKI without recovery group than in the no AKI or AKI with recovery group (Table 1).

**Changes in the BNP level and fluid status parameters**

The delta-BNP levels from D0 to D1, change in body weight from D0 to D1, fluid accumulation on D1, fluid accumulation on D2, and fluid accumulation during the entire ICU stay were lower in the no AKI or AKI with recovery group (Figures 2A–2E). The delta-BNP level from D0 to D1 was significantly correlated with the delta-central venous pressure levels (Figure S1), but there was no correlation between the delta-BNP level (from D0 to D1) and fluid accumulation on D1 (Figure 2F).

Among the septic patients, the no AKI or AKI with recovery group had lower BNP levels on D0, D1, and D2, smaller delta-BNP levels from D0 to D1, lower fluid accumulation on D1 and during the ICU stay, compared to the AKI without recovery group (Figures 3A–3F).

**Predictors of better renal outcome (i.e., no AKI or AKI with recovery)**

We found that a change of < 81.8% in the delta-BNP level from D0 to D1 could remarkably predict a better renal outcome independently [odds ratio (OR), 17.21; \( p = 0.013 \); sensitivity = 92.7%, specificity = 80.7%]. Other predictors included a WBC from 8954/\( \mu \)L to 27,663/\( \mu \)L (OR, 9.88; \( p = 0.001 \)), hemoglobin level (Hb) of \( \geq 12.2 \) g/dL (OR, 6.53; \( p = 0.020 \); sensitivity = 65.0%; specificity = 84.6%), serum sodium level from 118 mmol/L to 145 mmol/L (OR, 6.00; \( p = 0.047 \)), heart rate (OR, 0.96; \( p = 0.013 \)), and APACHE II score (OR, 0.88; \( p = 0.007 \); Table 2). Traditional fluid status parameters such as fluid accumulation during the entire ICU stay \( (p = 0.081) \) was not a significant predictor of no AKI or AKI recovery. In the final multivariate regression analysis, these parameters yielded a predictive model with good discriminative power. The area under the receiver operating characteristic curve was 0.896.

**Subgroup analysis for better renal outcome: Interaction between fluid status parameters and sepsis**

In the subgroup analysis of patients with sepsis, we found significant interactions between the delta-BNP levels and sepsis and between fluid accumulation during the ICU stay and sepsis (Table 3). In septic patients, a change in the delta-BNP levels of \( > 81.8\% \) from D0 to D1 was associated with AKI occurrence and decreased probability of recovery \( (p = 0.003; \text{ sensitivity } = 89.5\%; \text{ specificity } = 91.0\%) \). In nonseptic patients, greater fluid accumulation during the ICU stay was associated with AKI occurrence and decreased probability of recovery \( (p = 0.017) \).

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**Figure 2**  (A) Percent change in the BNP level from D0 to D1 between the AKI without recovery group and the no AKI or AKI with recovery group. (B) Change in the BW from D0 to D1. (C) Fluid accumulation on D1. (D) Fluid accumulation on D1. (E) Fluid accumulation during the ICU stay. (F) The correlation scatter plot of the percent change in the BNP level from D0 to D1 and fluid accumulation on D1. *\( p < 0.01 \). AKI = acute kidney injury; BNP = brain natriuretic peptide; BW = body weight; D0 = Day 0 (i.e., on ICU admission); D1 = Day 1; D2 = Day 2; ICU = intensive care unit.
Predictors of mortality

Delta-BNP levels from D0 to D1 ($p = 0.004$) were independently associated with ICU mortality (Table 4). Other predictors included malignancy ($p = 0.030$), age $\geq 58$ years ($p = 0.012$, sensitivity $= 69.0\%$, specificity $= 84.3\%$), mean blood pressure $< 70$ mmHg or $\geq 113$ mmHg ($p = 0.040$), SOFA score ($p = 0.002$), serum creatinine level on ICU admission ($p = 0.050$), serum albumin level ($p < 0.001$), and use of inotropic or vasopressor drugs ($p = 0.015$).

Subgroup analysis for mortality: Interaction between fluid status parameters and sepsis

The delta-BNP levels and fluid accumulation during the ICU stay both interacted with sepsis (Table S2). In septic patients, delta-BNP levels from D0 to D1 ($p = 0.002$) and fluid accumulation ($p = 0.043$) were associated with mortality.

Discussion

Fluid resuscitation is the cornerstone of restoring hemodynamic stability and renal blood flow, which prevents the...
development of AKI and subsequent mortality. However, in patients with AKI, Bouchard et al.\(^5\) found that fluid overload, defined as more than a 10% increase in body weight relative to the baseline weight, resulted in greater mortality and less chance of renal function recovery. Teixeira et al.\(^16\) report that a more positive fluid balance was associated with 28-day mortality among patients with AKI. In the Finnish Acute Kidney Injury (FINNAKI) study,\(^17\) critically ill patients with fluid overload at the initiation of renal replacement therapy had twice the 90-day mortality, compared to patients without fluid overload.

However, many methods to guide fluid therapy are invasive and operator-dependent. For example, the central venous pressure (CVP) level and continuous pulse contour cardiac analysis catheter are widely used, although a systematic review has suggested these methods have a poor relationship with blood volume.\(^18,19\) By contrast, the sonographically obtained ratio of the inferior vena cava to aorta diameter index seems to be useful for estimating fluid responsiveness.\(^20\) Even so, it is operator-dependent, and evidence of its association with outcome is rare.\(^21\) Alternative instruments such as bioimpedance devices estimate extra- and intracellular fluid but these are only tested in the static phase such as among patients on chronic dialysis.\(^22\) It has not been widely studied in acutely ill patients.

In our opinion, optimal fluid status should not be determined only by arbitrary traditional parameters or absolute fluid volume. The optimal fluid status should be considered physiologically. It is influenced by many factors such as intravascular volume, vascular resistance, myocardial compliance and contractility, and capillary permeability.\(^9\) It is difficult to find a method that takes these factors into account; however, BNP level has the potential to meet these requirements. From a cardiovascular standpoint, the optimal fluid status is the condition under which the heart performs at its best.

### Table 3  Multivariate analysis of the predictors of no AKI or AKI with recovery in the subgroup analysis of patients with sepsis.\(^a\)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Estimated regression coefficient</th>
<th>Estimated standard error</th>
<th>z</th>
<th>p</th>
<th>Estimated OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>8.222</td>
<td>2.499</td>
<td>3.291</td>
<td>0.001</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>% Change in the BNP D01 ≥ 81.8% × Sepsis</td>
<td>-4.062</td>
<td>1.367</td>
<td>-2.973</td>
<td>0.003</td>
<td>0.02</td>
<td>&lt;0.01–0.25</td>
</tr>
<tr>
<td>Fluid accumulation during ICU stay × No sepsis</td>
<td>-0.002</td>
<td>0.001</td>
<td>-2.392</td>
<td>0.017</td>
<td>0.99</td>
<td>0.99–0.99</td>
</tr>
<tr>
<td>8954/(\mu L &lt; WBC &lt; 27663/(\mu L)</td>
<td>2.745</td>
<td>0.754</td>
<td>3.641</td>
<td>&lt;0.001</td>
<td>15.56</td>
<td>3.98–79.79</td>
</tr>
<tr>
<td>Hb ≥ 12.2 g/dL</td>
<td>2.182</td>
<td>0.866</td>
<td>2.524</td>
<td>0.012</td>
<td>8.87</td>
<td>1.89–58.41</td>
</tr>
<tr>
<td>118 mmol/L ≤ Na &lt; 145 mmol/L</td>
<td>2.032</td>
<td>0.953</td>
<td>2.132</td>
<td>0.033</td>
<td>7.63</td>
<td>1.22–57.02</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.051</td>
<td>0.018</td>
<td>-2.833</td>
<td>0.005</td>
<td>0.95</td>
<td>0.91–0.98</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>-0.150</td>
<td>0.047</td>
<td>-3.151</td>
<td>0.002</td>
<td>0.86</td>
<td>0.78–0.94</td>
</tr>
</tbody>
</table>

\(\text{APACHE II} = \text{Acute Physiology and Chronic Health Evaluation II}; \text{BNP} = \text{brain natriuretic peptide}; \text{CI} = \text{confidence interval}; \text{D01} = \text{change of in the brain natriuretic peptide level from Day 0 to Day 1}; \text{Hb} = \text{hemoglobin}; \text{ICU} = \text{intensive care unit}; \text{Na} = \text{serum sodium}; \text{OR} = \text{odds ratio}; \text{WBC} = \text{white blood count}.\)

\(^a\) Goodness-of-fit assessment: adjusted generalized \(R^2 = 0.581\) (i.e., > 0.3), the estimated area under the receiver operating characteristic (ROC) curve = 0.914 (i.e., > 0.7), and in the modified Hosmer–Lemeshow goodness-of-fit \(F\) test, \(p = 0.402\) (i.e., > 0.05; \(df = 9, 144\)). These findings indicate an excellent fit.

### Table 4  Multivariate analysis of the predictors of intensive care unit mortality fitting multiple logistic regression models using the stepwise variable selection method.\(^a\)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Estimated regression coefficient</th>
<th>Estimated standard error</th>
<th>z</th>
<th>p</th>
<th>Estimated OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-1.367</td>
<td>1.526</td>
<td>-0.901</td>
<td>0.370</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2.370</td>
<td>1.090</td>
<td>2.172</td>
<td>0.030</td>
<td>10.70</td>
<td>1.31–97.02</td>
</tr>
<tr>
<td>Age ≥ 58 y</td>
<td>1.823</td>
<td>0.727</td>
<td>2.511</td>
<td>0.012</td>
<td>6.19</td>
<td>1.64–29.21</td>
</tr>
<tr>
<td>MBP &lt; 70 mmHg or ≥ 113 mmHg</td>
<td>1.149</td>
<td>0.558</td>
<td>2.064</td>
<td>0.040</td>
<td>3.15</td>
<td>1.07–9.77</td>
</tr>
<tr>
<td>SOFA score</td>
<td>0.335</td>
<td>0.111</td>
<td>3.032</td>
<td>0.002</td>
<td>1.40</td>
<td>1.14–1.77</td>
</tr>
<tr>
<td>Serum creatinine level on ICU admission (mg/dL)</td>
<td>0.250</td>
<td>0.127</td>
<td>1.963</td>
<td>0.050</td>
<td>1.28</td>
<td>1.00–1.70</td>
</tr>
</tbody>
</table>

\(\text{BNP} = \text{brain natriuretic peptide}; \text{CI} = \text{confidence interval}; \text{ICU} = \text{intensive care unit}; \text{MBP} = \text{mean blood pressure}; \text{OR} = \text{odds ratio}; \text{SOFA} = \text{SOFA, Sequential Organ Failure Assessment}.\)

\(^a\) Goodness-of-fit assessment: adjusted generalized \(R^2 = 0.581\) (i.e., > 0.3), the estimated area under the receiver operating characteristic (ROC) curve = 0.914 (i.e., > 0.7); and in the modified Hosmer–Lemeshow goodness-of-fit \(F\) test, \(p = 0.3628\) (i.e., > 0.05; \(df = 9, 144\)). These findings indicate an excellent fit.
Brain natriuretic peptide has been proven useful for predicting the prognosis of heart failure, and the addition of N-terminal pro-B-type natriuretic peptide (NT-proBNP)-guided therapy improves clinical outcomes in patients with heart failure. Furthermore, BNP may be used to predict mortality and to guide fluid management in hemodialysis patients.

In our study, we chose BNP because of its short half-life and relative independence from the glomerular filtration rate and patient's age, compared to NT-proBNP. report that increased BNP levels are associated with AKI development on ICU admission or during the ICU stay. Our patients with AKI without recovery also had significantly higher BNP levels on D1 and D2. In addition, other traditional, noninvasive fluid status parameters such as change in the body weight and fluid accumulation were also higher in the group with poor renal outcomes (Figure 2). However, delta-BNP levels from D0 to D1 were not correlated with fluid accumulation on D1. In multivariate analysis, the delta-BNP level, rather than fluid accumulation or weight change, was significantly associated with renal outcome and mortality. This finding indicates that the delta-BNP level is a better predictor than the absolute BNP level or traditional fluid status parameters, which were significant predictors in other studies. We suggest two main reasons for the association between positive delta-BNP levels and poor renal outcome. First, volume overload resulted in BNP secretion and interstitial edema and renal damage. Second, more severe renal damage induced fluid retention and BNP production. Most importantly, we found that the cutoff level of 98.1% in the change in delta-BNP levels from D0 to D1 could predict a better renal outcome (Figure S2). Therefore, the delta-BNP level may be a useful marker as guidance for the initial fluid resuscitation to improve renal outcome. This hypothesis should be confirmed by randomized studies in the future.

With regard to other predictors of the better renal outcome in our study, patients with white blood cell counts ranging from 8954/μL to 27,663/μL had adequate immune responses, and their diseases were not so severe as to induce extreme leukocytosis. This finding was compatible with a recent study that showed a U-shaped relationship for white blood cell count and AKI. A higher hemoglobin level resulted in better outcomes because it acted as a reserve for renal blood flow and oxygenation. Serum sodium levels ranging from 118 mmol/L to 145 mmol/L predicted better renal outcomes, compared to sodium levels outside this range. Many studies demonstrate that severe hypo- and hypernatremia represent inadequate fluid status and are independent risk factors for mortality. Additional factors associated with poor renal outcome included higher APACHE II scores and higher heart rate, which indicated severe disease.

In septic patients, an elevated BNP level is a proven predictor of mortality. Septic patients with poor renal outcomes also had elevated BNP levels at the beginning of their ICU stay (Figure 3). Because volume resuscitation is an important treatment for sepsis, the International Surviving Sepsis Campaign Guidelines Committee recommends fluid management to achieve a target CVP level. However, the CVP level was not a predictor for outcomes in our study and had a poor relationship with volume status and hemodynamic response. As a result, we performed a subgroup analysis and determined that delta-BNP levels from D0 to D1 remained a significant predictor of renal outcome among our septic patients. These results could stimulate more investigations into the application of the BNP level in the fluid management of septic patients.

Regarding the risk factors of mortality, in contrast to other studies in which BNP level at ICU admission was an independent prognostic marker, we found that a change in the delta-BNP levels from D0 to D1 resulted in higher risk of death. Fluid accumulation was associated with mortality in one report; however, the change in delta-BNP levels from D0 to D1 was a better predictor of mortality than fluid accumulation. Furthermore, in our analysis and in other studies, cancer patients had a higher mortality. In addition, old age has long been associated with mortality. Similar to other studies, a lower serum albumin level is also a prognostic marker of death. Use of inotropic or vasopressor agents has traditionally been regarded as a risk factor of death. However, it was interesting that the use of inotropic or vasopressor drugs was a beneficial predictor in our study. This finding may be because our patients without inotropic or vasopressor agent usage had more severe disease such as respiratory failure. Even if they did not use inotropes, they had a greater average severity score.

With regard to other predictors, a lower mean blood pressure is a prognostic factor of mortality. Higher blood pressure can also have negative consequences on the heart and kidneys and is associated with mortality. In our subgroup analysis, delta-BNP levels from D0 to D1 remained a useful predictor of mortality in septic patients.

This prospective observational study had several limitations. First, the intensive care specialists determined the fluid management methods and the hemodynamic monitoring devices; therefore, not all patients had CVP data or information from invasively placed catheters. Second, the BNP level was checked only within the first 48 hours of the patients' ICU stay, and trends in BNP levels after the ICU stay could also be associated with patient outcomes. Third, patients with heart dysfunction were excluded in our study. However, under usual conditions, some patients admitted to the ICU had heart failure or acute coronary syndrome. Whether our results could be applied in these patients remains to be further evaluated.

In conclusion, a useful marker for renal outcome prediction and fluid management is a major issue in critical care. Our results demonstrated that the delta-BNP level rather than the absolute BNP levels or other traditional parameters was more capable in predicting outcomes in critically ill patients. delta-Brain natriuretic peptide levels of < 81.8% within 24 hours of ICU admission could independently predict a better renal outcome. Even in septic patients, the delta-BNP level remained a valuable predictor of renal outcome. The BNP level may be a biomarker for monitoring and helping to achieve optimal fluid status in critically ill patients.

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Brain natriuretic peptide and acute kidney injury

1195

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jfma.2015.10.015.

References


