NT-proBNP Is Predictive of the Weaning from Continuous Renal Replacement Therapy

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Continuous renal replacement therapy (CRRT) is a dialysis modality used to treat patients with severe acute kidney injury. Nevertheless, there is limited information on the predictors of weaning from CRRT. The present study examined whether the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) can predict weaning from CRRT, based on the fact that this cardiac neurohormone is known to predict kidney dysfunction. Plasma NT-proBNP and several other baseline parameters at the time of starting CRRT were retrieved from 160 patients. The odds ratio (OR) for weaning from the CRRT within two weeks was calculated using a multivariate stepwise logistic model. We calculated the cut off value predicting weaning outcome by using the receiver operating characteristic curve and corresponding Youden index, and then divided patients into high (n = 74) and low (n = 86) NT-proBNP groups. The high NT-proBNP group had a lower weaning rate than the low NT-proBNP group [adjusted OR, 0.36 (0.170-0.756); *P* = 0.007]. We additionally found other predictors of weaning, such as sex, serum creatinine, urine output, and the score from the Acute Physiology and Chronic Health Evaluation, but all of these were not better than NT-proBNP in the predictability of weaning outcome. Neutrophil gelatinase-associated lipocalin, a well-known biomarker of acute kidney injury and originating from kidney, was not related with the CRRT weaning, which indicated the usefulness of NT-proBNP in the cases of CRRT despite originating from heart. The present study addresses the potential of NT-proBNP as an independent predictor of weaning from CRRT.

Keywords: continuous renal replacement therapy; intensive care unit; NGAL; NT-proBNP; weaning

Introduction

Continuous renal replacement therapy (CRRT) is one of the dialysis modalities used to treat critically ill patients, particularly those with severe acute kidney injury (AKI). CRRT can easily control biochemical imbalances due to AKI. Because of this therapeutic efficiency and the increasing incidence of AKI, the use of CRRT has increased over the past few years (Hoste and Schurgers 2008). However, despite the wide use of CRRT, several issues, such as the worse outcome of AKI and an increasing prevalence of elderly patients and patients with multiple comorbidities (Turney 1996; Bagshaw et al. 2009), result in high morbidity and mortality in patients undergoing CRRT. Furthermore, CRRT has a limitation in the context of its economic burden to patients (Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group 2012). These features indicate that researchers need to study patients commencing CRRT to better understand CRRT-related factors and improve their outcomes, but such research has been relatively limited. In particular, there are no established guidelines for the initiation of or weaning from CRRT. This is different from the issue of mechanical ventilation, which has been studied in many multicenter randomized trials and for which several international consensus guidelines exist (Finkel and Podoll 2009). In this respect, further data on the use of CRRT are needed to give relevant information to clinicians.

Natriuretic peptide is a cardiac neurohormone originating from ventricular myocytes that is released in response to ventricular dysfunction and increased myocardial stress (Kinnunen et al. 1993). The natriuretic peptides released are divided into two subtypes: the biologically inert amino-terminal fragment, called N-terminal prohormone of brain natriuretic peptide (NT-proBNP), and the biologically active BNP. NT-proBNP is more stable, has a longer half-

life, and may be a better biomarker for heart failure than BNP (Panteghini and Clerico 2004). Accordingly, NT-proBNP has been widely investigated in the field of heart disease (James et al. 2003; Pfister et al. 2008). Intriguingly, NT-proBNP also has predictive value for diseases of other organs, including kidney dysfunction (Colbert et al. 2015). Its predictive value is useful for determining both the outcomes of critically ill patients (Christenson 2008) and for the likelihood of being weaned from mechanical ventilation (Determann et al. 2013). However, the relationship between NT-proBNP and the weaning from CRRT has not been examined. We herein sought to address whether the NT-proBNP level at the time of starting CRRT can predict weaning from CRRT, using a prospectively recruited cohort. Furthermore, we compared the predictive value of NT-proBNP with that of plasma neutrophil gelatinase-associated lipocalin (NGAL), which is a well-known biomarker of AKI (Devarajan 2010).

Methods

Participants and data collection

Data on patients commencing CRRT were obtained retrospectively from a prospectively recruited cohort from a tertiary referral center (Seoul National University Hospital). The inclusion criteria were as follows: CRRT was needed due to severe AKI and the patient's age was 18 years or older. Accordingly, a total of 669 patients were enrolled at the start of CRRT between May 2010 and September 2013. All of the patients who participated in the present study provided informed consent and agreed to undergo the baseline clinical and laboratory examination in adherence to the study protocol. Among these patients, the measurement of the NT-proBNP level was available for 257 patients, all of whom provided written informed consent for the donation and use of their blood in the present study. We excluded patients who were previously diagnosed with end-stage renal disease or who had received dialysis before enrollment (n = 97). Consequently, 160 patients were analyzed for the present study.

Clinical parameters, such as patient age, sex, weight, cause of AKI, dialysis dose, the need for mechanical ventilation, the use of vasoactive drugs, and the underlying chronic kidney disease, were recorded at the start of CRRT. The causes of AKI were divided into sepsis, surgery, nephrotoxins, and others. Information on comorbidities was collected and was presented as the Charlson Comorbidity Index (Charlson et al. 1987). The Acute Physiology and Chronic Health Evaluation (APACHE) II score was calculated to quantitatively assess each patient's status (Knaus et al. 1985). Blood parameters such as the hemoglobin, blood urea nitrogen, creatinine, albumin, and sodium levels were measured, and the urine output data during the first two hours of CRRT were recorded. The target dose at the time of initiating CRRT was determined based on each patient's state. The plasma NT-proBNP and NGAL levels were measured using an electrochemiluminescence immunoassay (Cobas E 411 Analyzer, Roche Diagnostics, Mannheim, Germany) and an enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA), respectively. For NT-proBNP, the maximum measurable value was 35,000 pg/mL. There were no missing data for any of the variables. The primary outcome was weaning from CRRT within two weeks. The reason of stopping CRRT was due to the complete or partial recovery from AKI. All patients were followed until death or hospital discharge.

The study protocol complied with the Declaration of Helsinki and received full approval from the institutional review board of Seoul National University Hospital (no. H-1412-031-631).

Statistical analysis

The data are presented as the means ± standard deviations for the continuous variables and as the proportions for the categorical variables. The variables with non-normal distributions are expressed as the medians [interquartile range (IQR)] based on variable distributions using histograms. The chi-squared test was used to compare categorical variables. The comparisons between normally and non-normally distributed continuous variables were performed using Student's t-test and Mann-Whitney U test, respectively. We divided patients into high and low NT-proBNP groups, according to the best level related with the outcome. To find the best NT-proBNP level predicting weaning from CRRT, we used the Youden index of the receiver operating characteristic (ROC) curve (Youden 1950). Cumulative weaning curves were drawn using the Kaplan-Meier method. To compare the curves between the groups, the log-rank test was initially applied. To calculate the odds ratios (ORs) of the outcome, the logistic regression model was used with and without adjustments for the covariates. Covariates with non-normal distributions were adjusted after dividing the patients into two groups by median value. In the multivariate models, a backward stepwise selection method was used to prevent co-linearity among significant predictors. Cox proportional hazard model was also applied to calculate hazard ratio. The discrimination of predicting the CRRT weaning between parameters was assessed by calculating the area under the curve (AUC) of ROC. The comparison of AUCs was tested using a method described by DeLong et al. (1988). A value of $P < 0.05$ was considered significant. All analyses and calculations were performed using the SPSS software (version 21.0, IBM Corp., Chicago, IL, USA).

Results

Baseline characteristics

The baseline characteristics of the patients are shown in Table 1. For the 160 subjects, the mean age was 64 years. All of the subjects were of Asian descent. Approximately half of the patients received CRRT because of sepsis. The patients were weaned from CRRT after a median period of four days (IQR, 3-8 days).

Relationship between NT-proBNP and weaning from CRRT

Fig. 1 shows the histogram for the NT-proBNP at the time of starting CRRT. Forty-three patients (26.9%) had NT-proBNP levels ≥ 35,000 pg/mL. Based on this skewed distribution, we divided the patients into high and low NT-proBNP groups. The dividing point (15,767 pg/mL) was calculated using the Youden's index (Fig. 2). The baseline characteristics of the high and low NT-proBNP groups are shown in the Table 1. The two groups had similar baseline characteristics including the severity of illness and NGAL level. With regard to the outcome, the length of hospital stay was not different between the two groups: 11 days (IQR, 3-31 days) in the low level group and 10 days (IQR, 3-27 days) in the high level group; $P = 0.857$.

Table 1. Baseline characteristics of study subjects.

	Total (n = 160)	NT-proBNP level		P
		Low group (n = 86)	High group (n = 74)	
Age (years)	64.1 ± 15.42	63.5 ± 15.19	64.8 ± 15.75	0.576
Male sex (%)	59.4	60.5	58.1	0.762
Body weight (kg)	63.1 ± 11.39	63.4 ± 11.80	62.7 ± 10.96	0.729
Septic acute kidney injury (%)	53.1	58.1	47.3	0.171
Use of vasoactive drugs (%)	78.8	76.7	81.1	0.504
Chronic kidney disease (%)	44.4	43.0	45.9	0.711
Charlson Comorbidity Index	2.8 ± 1.97	2.6 ± 2.04	3.0 ± 1.88	0.155
APACHE II score	29.3 ± 8.78	29.2 ± 9.76	29.5 ± 7.54	0.859
Hemoglobin (g/dL)	9.7 ± 2.11	9.8 ± 2.29	9.6 ± 1.90	0.598
Blood urea nitrogen (mg/dL)*	54 (35.5-82.0)	53 (40.0-82.0)	57 (32.0-83.3)	0.902
Creatinine (mg/dL)*	2.9 (1.91-3.81)	2.9 (1.89-3.78)	3.1 (2.02-3.92)	0.542
Albumin (g/dL)	2.6 ± 0.52	2.6 ± 0.59	2.6 ± 0.42	0.781
Sodium (mmol/L)	135.5 ± 7.76	135.8 ± 6.79	135.1 ± 8.78	0.563
Urine output (mL/2 hours)*	20 (0-70)	20 (0-56)	25 (4-80)	0.331
Target dose (%)				0.262
≤ 40 mL/kg/hour	75.6	72.1	79.7	
> 40 mL/kg/hour	24.4	27.9	20.3	
NGAL (ng/mL)*	453.5 (256.3-858.6)	441.4 (239.1-850.3)	465.9 (260.3-895.9)	0.493
Duration of weaning CRRT (days)*	4 (3-8)	4 (2-6)	5 (3-9)	0.022

*Data are expressed as the median (interquartile range) when the distribution of data was skewed.
Target doses at the time of initiating CRRT were established based on the patients' clinical states.
NT-proBNP, N-terminal prohormone of brain natriuretic peptide; APACHE, Acute Physiology and Chronic Health Evaluation; NGAL, neutrophil gelatinase-associated lipocalin; CRRT, continuous renal replacement therapy.

Additionally, the two groups had similar in-hospital mortality rates: the OR in the high vs. low group was 1.42 (0.707-2.866) ($P = 0.322$).

We compared the Kaplan-Meier curves of the weaning rates between the high and low NT-proBNP groups (Fig. 3A). As a result, patients with low NT-proBNP levels were more likely to be weaned from CRRT than those with high levels ($P = 0.002$). Subsequently, we constructed logistic regression models to determine whether NT-proBNP significantly predicts the weaning from CRRT under the effects of other covariates (Table 2). In the univariate model, four parameters, including the NT-proBNP, use of vasoactive drugs, APACHE score, and urine output, were found to be significant predictors of weaning. After adjusting for covariates, the NT-proBNP, APACHE score, and urine output were still related with weaning from CRRT. The patient sex and creatinine level were additionally found to be significant predictors. In particular, the high NT-proBNP group had a 63% lower chance of weaning than the low NT-proBNP group. Although the weaning was determined at different timeframes, the predictability of NT-proBNP remained significant: adjusted ORs were 0.43 (0.194-0.949) and 0.46 (0.217-0.983) for 1 and 3 weeks, respectively (all Ps < 0.05). When Cox proportional hazard model was applied, the adjusted hazard ratio of the weaning was 0.45 (0.266-0.752) ($P = 0.002$), which confirms the results from our initial analysis. However, the NGAL level was not related with the weaning from CRRT in either the univariate or multivariate model, as shown in Fig. 3B.

Based on these results, we compared the area under the ROC curves for predicting CRRT weaning between significant continuous parameters (Table 3). The AUC of NT-proBNP was calculated as 0.579 (0.489-0.669); this value did not differ from the AUCs of other parameters, such as serum creatinine, urine output, and APACHE II score (all Ps > 0.5). The best model for predicting CRRT weaning was one that included NT-proBNP in addition to serum creatinine, urine output, and APACHE II score.
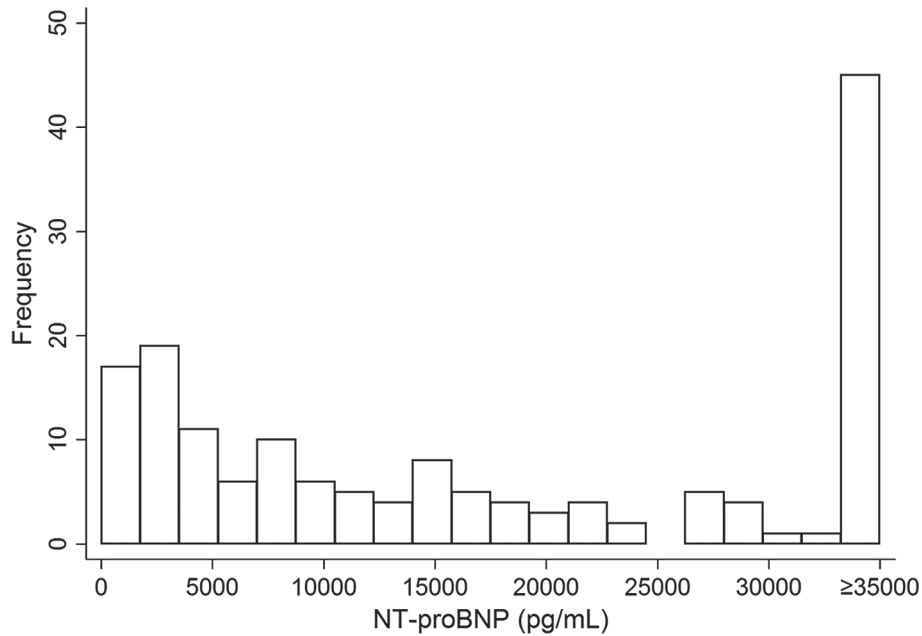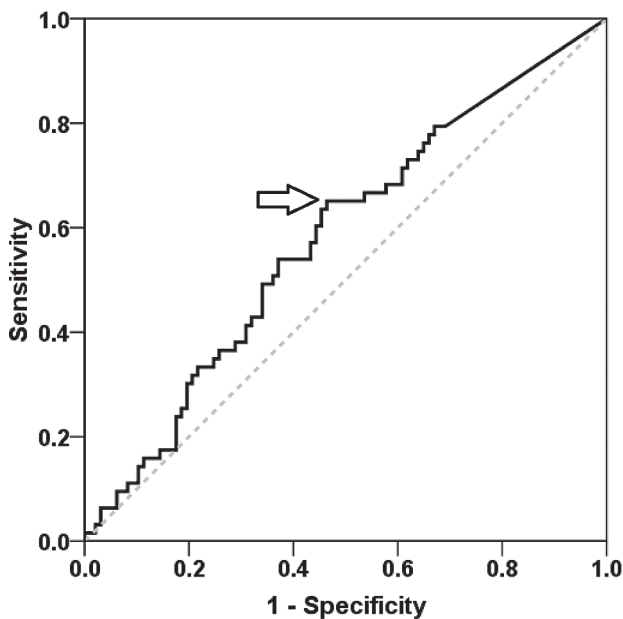
Fig. 1. A histogram of the NT-proBNP levels.

Fig. 2. Receiver operating characteristic curve depending on the value of NT-proBNP. The arrow indicates the best cut-off level for predicting weaning from continuous renal replacement therapy.

We further compared the survival rates between the weaning and non-weaning groups. As shown in Fig. 4, the survival rates were significantly different between two groups ($P < 0.001$). Hazard ratio of mortality was 15.96 (9.361-27.221) in the non-weaning group compared with the weaning group ($P < 0.001$).

Sensitivity analysis

The present weaning outcome might have been affected by the patients' mortality itself, as follows: if a case having a high weaning possibility died before weaning, the weaning predictability would have been altered. Accordingly, we conducted a sensitivity analysis that included only the surviving patients after weaning (n = 78). As a result, the high NT-proBNP group had a lower likelihood of weaning from CRRT than the low group: OR, 0.27 (0.081-0.884); $P = 0.031$. A multivariate logistic model showed that only two parameters, the NT-proBNP level and sex, were significant predictors: the OR of the high vs. low NT-proBNP groups was 0.20 (0.057-0.727) and the OR of females vs. males was 5.20 (1.236-21.903).

NT-proBNP is secreted from myocytes (Kinnunen et al. 1993). Thus, the NT-proBNP levels mainly reflect heart function (James et al. 2003; Pfister et al. 2008) even though relationships with other organ functions also exist (Medina et al. 2011; Colbert et al. 2015). Accordingly, heart function can affect the relationship between the NT-proBNP level and weaning outcome. To avoid the interaction of the heart function, we reviewed the echocardiographic data on the ejection fractions, all of which were examined at the time of starting CRRT (n = 130), and we additionally adjusted for the ejection fraction in the logistic models. The ejection fraction (49.0% ± 14.67%) in the high NT-proBNP group was lower than that in the low group (57.1% ± 11.86%) ($P = 0.001$). When we included the ejection fraction in the multivariate model shown in Table 2, the NT-proBNP remained significant: the OR of the high vs. low groups was 0.36 (0.162-0.783) ($P = 0.010$). However, the ejection fraction was not related with the predictability of the weaning outcome.

Discussion

CRRT is an important treatment option, particularly for patients with a shutdown of kidney function. Despite
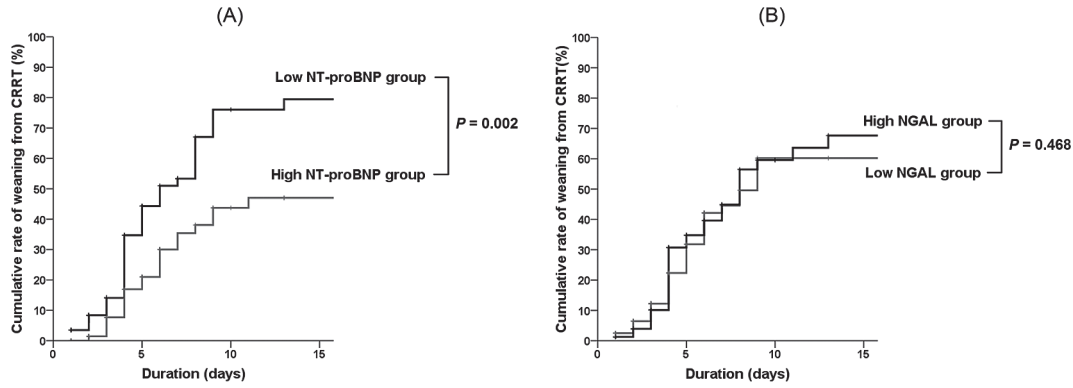
Fig. 3. Kaplan-Meier curves for the weaning outcome in the high and low level groups. (A), NT-proBNP; (B), NGAL.

Table 2. Predictability of weaning from continuous renal replacement therapy.

Variables	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (per 1 year)	0.99 (0.971-1.011)	0.382		
Male sex (vs. female)	0.56 (0.292-1.063)	0.076	0.36 (0.165-0.772)	0.009
Body weight (per 1 kg)	0.99 (0.958-1.014)	0.315		
Septic acute kidney injury (vs. others)	0.86 (0.454-1.618)	0.634		
Use of vasoactive drugs (vs. none)	0.36 (0.167-0.788)	0.010		
Chronic kidney disease (vs. none)	1.24 (0.656-2.350)	0.506		
Charlson Comorbidity Index (per 1 score)	0.92 (0.778-1.081)	0.301		
APACHE II score (per 1 score)	0.92 (0.880-0.963)	< 0.001	0.91 (0.862-0.956)	< 0.001
Hemoglobin (per 1 g/dL)	1.01 (0.872-1.177)	0.865		
High blood urea nitrogen (vs. low)	1.12 (0.595-2.118)	0.720		
High creatinine (vs. low)	1.79 (0.941-3.396)	0.076	3.15 (1.447-6.871)	0.004
Albumin (per 1 g/dL)	1.50 (0.804-2.808)	0.202		
Sodium (per 1 mmol/L)	1.00 (0.960-1.042)	0.992		
High NGAL (vs. low)	0.95 (0.503-1.790)	0.871		
High urine output (vs. low)	2.32 (1.209-4.434)	0.011	2.78 (1.324-5.857)	0.007
Target dose of > 40 mL/kg/hour (vs. ≤ 40)	1.45 (0.698-3.003)	0.320		
High NT-proBNP (vs. low)	0.46 (0.241-0.893)	0.021	0.37 (0.178-0.787)	0.010

The ranges of categorized covariates are as follows (units are skipped): blood urea nitrogen, 8 to 53 (low) vs. 54 to 157 (high); creatinine, 0.57 to 2.92 (low) vs. 2.96 to 17.36 (high); NGAL, 11.3 to 450.6 (low) vs. 456.3 to 8,459.0 (high); urine output, 0 to 20 (low) vs. 25 to 750 (high); target dose of dialysis, 20 to 40 vs. 50 to 100; and NT-proBNP, 14.4 to 15,680.0 (low) vs. 15,767.0 to ≥ 35,000.0 (high).
OR, odds ratio; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

CRRT's necessity in clinical practice, weaning-related factors for CRRT have not been thoroughly studied. With this regard, the present study has clinical implications for the following issues. First, the present data are the first report of the relationship between the NT-proBNP level at the start of CRRT and the weaning outcome. Second, this relationship was not affected by other outcomes such as length of hospital stay and mortality. Third, neither NGAL (a well-known biomarker of AKI) nor heart function (showing a similar trend to NT-proBNP in patients with heart disease) predicted the weaning from CRRT.

Many parameters for the weaning from mechanical

Table 3.   Area under the receiver operating characteristic curves for predicting weaning from continuous renal replacement therapy.

	AUC (95% CI)	P
NT-proBNP	0.579 (0.489-0.669)	Reference
Serum creatinine	0.589 (0.498-0.681)	0.875
Urine output	0.634 (0.549-0.720)	0.393
APACHE II score	0.663 (0.580-0.746)	0.163
Cr+UO+APACHE	0.680 (0.598-0.762)	0.092
NT-proBNP+Cr+UO+APACHE	0.701 (0.619-0.782)	0.007

NT-proBNP, N-terminal prohormone of brain natriuretic peptide; APACHE, Acute Physiology and Chronic Health Evaluation; Cr, creatinine; UO, urine output.
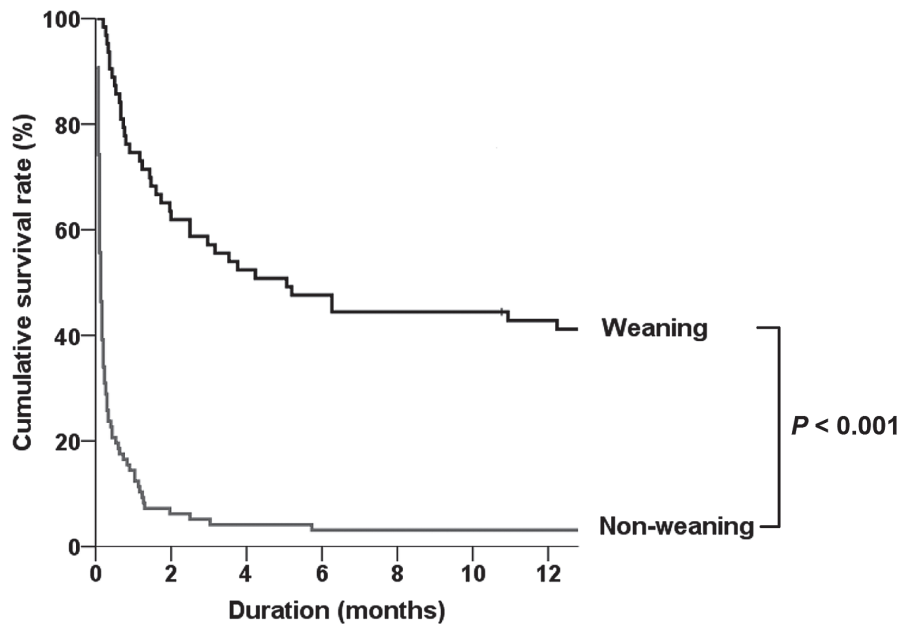

Fig. 4. Survival curves from the weaning and non-weaning groups from the continuous renal replacement therapy. Black, weaning group; Gray, non-weaning group.

ventilation have been revealed, ranging from the patient's baseline characteristics to ventilator-related issues (Thille et al. 2013). In particular, some studies have focused on the role of NT-proBNP in the weaning from mechanical ventilation (Determann et al. 2013; Zhang et al. 2014). In contrast to efforts in the field of mechanical ventilation, few studies have been conducted regarding the CRRT weaning (Uchino et al. 2009; Heise et al. 2012). A previous observational study has found that both the urine output and serum creatinine level at the time of CRRT discontinuation were associated with a low risk of repeat CRRT (Uchino et al. 2009). Another observational study has revealed that previous CRRT cycles, the Sequential Organ Failure Assessment score, and urine output after cessation of CRRT affected the outcome of CRRT-free interval (Heise et al. 2012). These studies focused on the factors observed during CRRT or at the end of CRRT, not at the initiation of CRRT. The present study sought to address the predictors at the time of starting CRRT, and found that the NT-proBNP

level was significant, in addition to previously known factors, including the urine output and severity of illness. We suggest that assessing these factors at the beginning of CRRT may provide more relevant information to clinicians than assessments made at other times.

The relationship between the NT-proBNP level and weaning from CRRT can potentially be explained by following mechanisms. Due to its origin, a high NT-proBNP level is associated with fluid overload (Paniagua et al. 2010). This issue is critical because fluid overload is a direct target of CRRT and also affects the outcome and efficiency of CRRT (Pannu and Gibney 2005; Vaara et al. 2012). Second, the high NT-proBNP level reflects cardiac dysfunction (James et al. 2003; Pfister et al. 2008), which may affect the weaning outcome because cardiac recovery leads to the early recovery of kidney function (Cruz 2013). However, our analysis showed that the effect of NT-proBNP on the weaning outcome was independent of and greater than that of cardiac functions. This suggests that the

NT-proBNP level may be a composite marker of the dysfunction of several organs. In particular, NT-proBNP is related with the kidney function (Colbert et al. 2015). However, the predictability of NT-proBNP in the present study remained significant irrespective of kidney function, such as urine output. All of these issues support the prognostic importance of NT-proBNP for the weaning from CRRT.

NGAL is a representative biomarker for early AKI, and thus, several studies have examined the prognostic value of NGAL in patients with AKI (Devarajan 2010; van Deursen et al. 2014). However, the present study did not find any relationship between NGAL and weaning from CRRT. This may be because we enrolled only patients with severe AKI, which led to a skewed distribution in the context of kidney function. Although we did not assess other biomarkers of AKI, such as kidney injury molecule-1 or N-acetyl-β-D-glucosaminidase, certain procedures or clinical status (i.e., status of CRRT) require clinicians to consider several factors not originating from kidney, and a notable example may be the NT-proBNP.

Although the present data are informative, this study has some limitations. First, the study design involved observing correlations, and this precluded us from drawing conclusions based on causality. However, the main aim of the present study was to determine the relationship itself. Thus, the current design does not significantly hamper this aim. Second, we did not retrieve important variables (e.g., the weaning method and the change of each parameter), which could affect the overall outcome. Third, the single center design requires that the data be validated in other cohorts. Despite this limitation, it is meaningful that the present results can form a basis for later studies focusing the role of NT-proBNP or the weaning-related factors for CRRT.

Data on the CRRT-related factors, including weaning, have been under-evaluated. This issue should be much evaluated because successful weaning affects the patient's outcome including survival. In this regard, it may be a great concern that NT-proBNP is a weaning-related factor. Future follow-up studies are needed to support the present findings and to address additional issues related with CRRT, all of which can eventually improve the clinical outcomes of CRRT.

Acknowledgments

Conflict of Interest

The authors declare no conflict of interest.

References

Bagshaw, S.M., Webb, S.A., Delaney, A., George, C., Pilcher, D., Hart, G.K. & Bellomo, R. (2009) Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. *Crit. Care*, **13**, R45.

Charlson, M.E., Pompei, P., Ales, K.L. & MacKenzie, C.R. (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.*, **40**, 373-383.

Christenson, R.H. (2008) What is the value of B-type natriuretic peptide testing for diagnosis, prognosis or monitoring of critically ill adult patients in intensive care? *Clin. Chem. Lab. Med.*, **46**, 1524-1532.

Colbert, G., Jain, N., de Lemos, J.A. & Hedayati, S.S. (2015) Utility of traditional circulating and imaging-based cardiac biomarkers in patients with predialysis CKD. *Clin. J. Am. Soc. Nephrol.*, **10**, 515-529.

Cruz, D.N. (2013) Cardiorenal syndrome in critical care: the acute cardiorenal and renocardiac syndromes. *Adv. Chronic Kidney Dis.*, **20**, 56-66.

DeLong, E.R., DeLong, D.M. & Clarke-Pearson, D.L. (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*, **44**, 837-845.

Determann, R.M., Royakkers, A.A., Schaefers, J., de Boer, A.M., Binnekade, J.M., van Straalen, J.P. & Schultz, M.J. (2013) Serum levels of N-terminal proB-type natriuretic peptide in mechanically ventilated critically ill patients: relation to tidal volume size and development of acute respiratory distress syndrome. *BMC Pulm. Med.*, **13**, 42.

Devarajan, P. (2010) Neutrophil gelatinase-associated lipocalin: a promising biomarker for human acute kidney injury. *Biomark. Med.*, **4**, 265-280.

Finkel, K.W. & Podoll, A.S. (2009) Discontinuation of continuous renal replacement therapy: when is enough enough? *Crit. Care Med.*, **37**, 2664-2665.

Heise, D., Gries, D., Moerer, O., Bleckmann, A. & Quintel, M. (2012) Predicting restoration of kidney function during CRRT-free intervals. *J. Cardiothorac. Surg.*, **7**, 6.

Hoste, E.A. & Schurgers, M. (2008) Epidemiology of acute kidney injury: how big is the problem? *Crit. Care Med.*, **36**, S146-S151.

James, S.K., Lindahl, B., Siegbahn, A., Stridsberg, M., Venge, P., Armstrong, P., Barnathan, E.S., Califf, R., Topol, E.J., Simoons, M.L. & Wallentin, L. (2003) N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation*, **108**, 275-281.

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. *Kidney Int. Suppl.*, **2**, 1-138.

Kinnunen, P., Vuolteenaho, O. & Ruskoaho, H. (1993) Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. *Endocrinology*, **132**, 1961-1970.

Knaus, W.A., Draper, E.A., Wagner, D.P. & Zimmerman, J.E. (1985) APACHE II: a severity of disease classification system. *Crit. Care Med.*, **13**, 818-829.

Medina, A.M., Marteles, M.S., Saiz, E.B., Martinez, S.S., Laiglesia, F.R., Rodriguez, J.A. & Perez-Calvo, J.I. (2011) Prognostic utility of NT-proBNP in acute exacerbations of chronic pulmonary diseases. *Eur. J. Intern. Med.*, **22**, 167-171.

Paniagua, R., Ventura, M.D., Avila-Diaz, M., Hinojosa-Heredia, H., Mendez-Duran, A., Cueto-Manzano, A., Cisneros, A., Ramos, A., Madonia-Juseino, C., Belio-Caro, F., Garcia-Contreras, F., Trinidad-Ramos, P., Vazquez, R., Ilabaca, B., Alcantara, G., et al. (2010) NT-proBNP, fluid volume overload and dialysis modality are independent predictors of mortality in ESRD patients. *Nephrol. Dial. Transplant.*, **25**, 551-557.

Pannu, N. & Gibney, R.N. (2005) Renal replacement therapy in the intensive care unit. *Ther. Clin. Risk Manag.*, **1**, 141-150.

Panteghini, M. & Clerico, A. (2004) Understanding the clinical biochemistry of N-terminal pro-B-type natriuretic peptide: the prerequisite for its optimal clinical use. *Clin. Lab.*, **50**, 325-331.

Pfister, R., Diedrichs, H., Schiedermair, A., Rosenkranz, S., Hellmich, M., Erdmann, E. & Schneider, C.A. (2008) Prognostic impact of NT-proBNP and renal function in comparison to contemporary multi-marker risk scores in heart failure patients. *Eur. J. Heart Fail.*, **10**, 315-320.

Thille, A.W., Richard, J.C. & Brochard, L. (2013) The decision to extubate in the intensive care unit. *Am. J. Respir. Crit. Care Med.*, **187**, 1294-1302.

Turney, J.H. (1996) Acute renal failure: a dangerous condition. *JAMA*, **275**, 1516-1517.

Uchino, S., Bellomo, R., Morimatsu, H., Morgera, S., Schetz, M., Tan, I., Bouman, C., Macedo, E., Gibney, N., Tolwani, A., Straaten, H.O., Ronco, C. & Kellum, J.A. (2009) Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. *Crit. Care Med.*, **37**, 2576-2582.

Vaara, S.T., Korhonen, A.M., Kaukonen, K.M., Nisula, S., Inkinen, O., Hoppu, S., Laurila, J.J., Mildh, L., Reinikainen, M., Lund, V., Parviainen, I. & Pettila, V. (2012) Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. *Crit. Care*, **16**, R197.

van Deursen, V.M., Damman, K., Voors, A.A., van der Wal, M.H., Jaarsma, T., van Veldhuisen, D.J. & Hillege, H.L. (2014) Prognostic value of plasma neutrophil gelatinase-associated lipocalin for mortality in patients with heart failure. *Circ. Heart Fail.*, **7**, 35-42.

Youden, W.J. (1950) Index for rating diagnostic tests. *Cancer*, **3**, 32-35.

Zhang, Q., Shi, Z.Y., Luo, C.H., Wang, L., Zhang, S.S., Cheng, X.R., Zhang, Q., Xu, Q.Y., Guo, H.X., Cheng, X.Y. & Sheng, G.Y. (2014) Application of NT-proBNP in ventilator weaning for preterm infants with RDS. *Pediatr. Pulmonol.*, **49**, 757-763.