Original article

Plasma neutrophil gelatinase-associated lipocalin predicts major adverse cardiovascular events after cardiac care unit discharge

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ARTICLE INFO

Article history:
Received 10 March 2015
Accepted in revised form 15 May 2015
Available online 27 July 2015

Keywords:
Neutrophil gelatinase-associated lipocalin
Cardiac care unit
Adverse cardiac events
Brain natriuretic peptide

ABSTRACT

Background: Emerging acute kidney injury biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), have a high potential for predicting worsening renal function. Acute exacerbation of renal dysfunction has a great impact on the outcomes of cardiovascular patients in critical conditions. This study aimed to evaluate whether plasma NGAL can predict the mortality and major adverse cardiovascular events (MACEs) after discharge from the cardiac care unit (CCU).

Methods: Patients who were admitted to the CCU of the Tokyo University Hospital were prospectively enrolled (101 patients). Blood and urinary markers, including the blood NGAL, brain natriuretic peptide, creatinine, cystatin C, urinary albumin, N-acetyl-β-D-glucosaminidase, and L-type fatty acid-binding protein, were measured at CCU discharge. The primary outcome was MACEs until at least 6 months after CCU discharge.

Results: Thirty-five patients experienced MACEs (35%). Multivariate logistic analysis revealed that the plasma NGAL, length of CCU stay, and existence of diabetes and heart failure were independent predicting factors for MACEs. Patients with the highest NGAL at discharge (>75th percentile) showed a significantly higher risk of MACEs than those with the lowest NGAL (<25th percentile) (log-rank test; hazard ratio, 5.15; 95% confidence interval 1.84–18.20; p < 0.01).

Conclusion: Plasma NGAL at CCU discharge is a significant prognostic indicator of outcomes at 6 months in critically ill cardiac patients treated in a CCU.

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Introduction

Renal dysfunction has been widely recognized as an independent exacerbating factor for cardiovascular disease [1,2]. Both acute and chronic renal impairments during the clinical course of heart diseases, including heart failure and coronary artery disease, have been defined as cardio-renal syndrome [3]. Critically ill patients who required cardiac care unit (CCU) admission often experience acute kidney injury (AKI), which is diagnosed as worsening renal function (WRF) [4–7]. In these patients, severe hypotension, decreased cardiac output, and elevated central venous pressure cause acute renal insults. Furthermore, diagnostic and therapeutic interventions also cause renal injury; contrast agents used in percutaneous coronary intervention (PCI) can induce renal tubular damage, and diuretics used for heart failure management frequently cause intravascular hypovolemia and renal hypoperfusion.

To date, new AKI biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and L-type fatty acid-binding protein (L-FABP), have been studied...
intensively [8–11]. These markers are secreted from the damaged renal tubular cell by renal ischemia or exposure to nephrotoxic agents, and they are elevated during the acute phase of kidney injury before the glomerular filtration rate declines. The limitations of serum creatinine for the early detection of renal damage in AKI are well known [12]; thus, these new biomarkers will allow clinicians to detect renal injury earlier.

Blood and urine NGAL are emerging biomarkers for AKI. Their performance in the early detection of renal damage has been valuable in several AKI cohorts, including post-cardiac surgery AKI [13]. Recently, several clinical studies found that blood and urine NGAL can predict WRF, mortality, and major adverse events of cardiovascular diseases, including acute decompensated heart failure (ADHF) and acute coronary syndrome (ACS) [14–21]. In most studies, NGAL was evaluated in ADHF patients, although one study exclusively targeted a population with ST-elevation myocardial infarction [18]. However, the generalizability and reliability of new biomarkers should be evaluated in heterogeneous populations before clinical use. Predictive values of NGAL have been mostly reported in ADHF patients. However, critically severe patients treated in CCUs frequently have ACS in addition to ADHF. Moreover, blood and urine NGAL were usually measured at admission or before initiating treatment, such as diuretics administration [20] and PCI [18]. Only one study evaluated the performance of plasma NGAL measured at discharge [16]; yet, patients with acute myocardial infarction, active ischemia, and cardiogenic shock were excluded although these critically ill conditions are frequently observed in CCUs.

In the present study, we aimed to investigate the clinical use of plasma NGAL in CCUs, especially for predicting long-term outcomes. Thus, we evaluated whether plasma NGAL measured at CCU discharge can predict major adverse cardiac events (MACEs) at 6-month outcomes. We hypothesized that the measurement of plasma NGAL at this time point may enable a better risk stratification for long-term outcomes.

Methods

Study design and patient population

The present study consecutively enrolled patients who were admitted to the CCU of the Tokyo University Hospital (Tokyo, Japan) from December 2011 to July 2012. Informed consent was obtained from each participant or the participants’ legal representative. The study protocol, which adhered to the principles of the Declaration of Helsinki, was approved by The University of Tokyo’s Institutional Review Board. Patients were excluded if they had end-stage renal disease or died during their CCU stay and if there was any missing data at CCU discharge. Although no clear criteria for CCU admission exist, severe conditions that require mechanical circulatory support, pressors, mechanical ventilation or non-invasive positive pressure ventilation, and emergency cardiac interventions for ACS were considered for CCU admission based on the attending physician’s decision.

Data sampling

The following clinical variables were evaluated: age, sex, the diagnosis for CCU admission, and left ventricular ejection fraction (LVEF) as measured by transthoracic echocardiogram on admission day. Two-dimensional imaging examinations were performed in the standard apical four- and two-chamber views. These images estimated LVEF using the modified, single-plane Simpson method. Ischemic heart disease was diagnosed when coronary artery stenosis was demonstrated by catheter coronary angiography during the CCU stay. Diagnosis of heart failure was determined according to the Framingham criteria [22]. Treatments during CCU admission included mechanical ventilation, intravenous inotropic agents, and induction of mechanical devices such as intra-aortic balloon pump were also recorded. Attending cardiologists discharged patients from the CCU when patients were hemodynamically stable and asymptomatic. The duration of the CCU stay and the entire hospitalization period were also recorded.

Blood and urine samples were obtained at CCU discharge. The following biomarkers were measured: plasma NGAL and N-terminal pro-brain natriuretic peptide (NT-proBNP), serum creatinine, cystatin C, BNP, urinary albumin, N-acetyl-β-D-glucosaminidase (NAG), and L-FABP. The values of the urinary biomarkers were normalized to the urinary creatinine concentration. For the plasma NGAL and NT-proBNP measurements, the Triage NGAL Test and the Triage NT-proBNP Test (Alere Medical Inc., San Diego, CA, USA) were used respectively. Other biomarkers were measured as previously described [23,24]. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation, which was adjusted for the Japanese population [25].

WRF was defined as more than a 1.5-fold increase of serum creatinine from baseline during the hospital stay. The baseline serum creatinine was defined as the minimum among the outpatient value within 6 months before admission, the inpatient value before admission, and the last value before discharge. For a patient with no creatinine measurement within the past 6 months, the baseline was defined as the minimum among the last value before discharge and the estimated value using the Modification of Diet in Renal Disease equation for the lower end of the reference range (i.e. 75 ml/min/1.73 m²), as the Kidney Disease International Global Outcomes guideline suggested [26].

Endpoints of the study

The enrolled patients were followed by reviewing their medical records until at least 6 months after CCU discharge. The follow-up period in the present study was 248.5 ± 118.9 [258 (178–342)] days. The primary endpoint was the incidence of a MACE, which consisted of all-cause mortality, emergent readmission, and coronary revascularization during the follow-up period. Coronary revascularization included either elective or emergent PCI or coronary artery bypass graft during the follow-up period.

Statistical methods

Continuous data are represented as mean ± standard deviation or median (interquartile). Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using the Pearson χ² or Fisher’s exact test. Step-wise multivariate logistic regression analysis was conducted to identify the predictors of MACEs. The following parameters were adopted in the analysis: biomarkers (plasma NGAL, NT-proBNP, creatinine, eGFR, BNP, cystatin C, urinary albumin, NAG, and L-FABP) and background or therapeutic characteristics (history of hypertension, dyslipidemia, diabetes mellitus, smoking, PCI, and coronary artery bypass grafting, height, body weight, LVEF, ischemic heart disease, ADHF, mechanical ventilation use, vasoactive/inotropic agents use, revascularization during CCU stay, and duration of CCU stay). The receiver operating characteristics (ROC) curve of each parameter for predicting the endpoint was drawn, and the cut-off points were determined at which the Youden index (sensitivity + specificity – 1) was maximized. The areas under the ROC curve were compared by the method previously described [27]. The cumulative event-free rate curve of each group was drawn in the Kaplan–Meier manner and was compared using the log-rank test or Wilcoxon test.
A p-value <0.05 was employed as the threshold of statistical significance. These statistical calculations were performed using the JMP software, version 9.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics and outcomes

One hundred and twenty-seven patients were admitted to the CCU during the study period. Twenty-six patients met the exclusion criteria; 5 patients died during CCU stay; 8 patients were on regular hemodialysis at CCU discharge; and 13 were excluded because of missing data. Finally, 101 patients were enrolled. The underlying etiologies for CCU admission are shown in Supplementary Table 1. During the 6-month follow-up period, 35 patients (35%) were classified as positive for the primary endpoint of the MACEs. Among those, there were 8 deaths, 20 emergent hospitalizations, and 10 coronary revascularizations during the follow-up period (Fig. 1). The precise event data are shown in Supplementary Table 2.

Table 1 shows the patient baseline characteristics before CCU discharge. Patients who developed MACEs were significantly older and complicated with diabetes more frequently. The prevalence of ADHF was significantly higher in the MACE group than in the non-MACE group. Although WRF was observed at a similar frequency in the MACE group and in the non-MACE group (40.0% vs. 30.3%, p = 0.33), the plasma NGAL values at CCU discharge responded to WRF with statistical significance (Fig. 2). Although WRF occurred after coronary revascularization in 5 patients, their NGAL levels were not higher than those of all the patients (Supplementary Table 3).

<table>
<thead>
<tr>
<th>Age, years</th>
<th>All patients (n=101)</th>
<th>MACE (+) (n=35)</th>
<th>MACE (-) (n=66)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>68.5 ± 12.8</td>
<td>72.9 ± 10.4</td>
<td>66.2 ± 13.4</td>
<td>0.022</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>59.7 ± 14.4</td>
<td>56.9 ± 14.0</td>
<td>61.1 ± 14.4</td>
<td>0.12</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>72 (71%)</td>
<td>28 (80%)</td>
<td>44 (67%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>30 (30%)</td>
<td>16 (46%)</td>
<td>14 (21%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>61 (60%)</td>
<td>23 (66%)</td>
<td>38 (58%)</td>
<td>0.43</td>
</tr>
<tr>
<td>History of PCI, %</td>
<td>18 (18%)</td>
<td>7 (20%)</td>
<td>11 (17%)</td>
<td>0.68</td>
</tr>
<tr>
<td>History of CABG, %</td>
<td>3 (3%)</td>
<td>1 (2.9%)</td>
<td>2 (3.0%)</td>
<td>0.96</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>54 (53%)</td>
<td>17 (49%)</td>
<td>37 (56%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>51.3 ± 16.3</td>
<td>49.8 ± 17.9</td>
<td>52.1 ± 15.3</td>
<td>0.60</td>
</tr>
<tr>
<td>Ischemic heart disease confirmed by CAG, %</td>
<td>52 (51%)</td>
<td>18 (51%)</td>
<td>34 (52%)</td>
<td>0.99</td>
</tr>
<tr>
<td>ADHF, %</td>
<td>48 (48%)</td>
<td>24 (69%)</td>
<td>24 (36%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mechanical ventilation, %</td>
<td>12 (12%)</td>
<td>5 (14%)</td>
<td>7 (11%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Vasoactive/inotropic agents, %</td>
<td>24 (24%)</td>
<td>9 (26%)</td>
<td>15 (23%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Revascularization during the CCU stay, %</td>
<td>48 (49%)</td>
<td>13 (37%)</td>
<td>35 (53%)</td>
<td>0.13</td>
</tr>
<tr>
<td>CCU stay, d</td>
<td>5 (3.5–9)</td>
<td>6 (4–8)</td>
<td>5 (3–9)</td>
<td>0.38</td>
</tr>
<tr>
<td>Whole period of the hospitalization, d</td>
<td>20 (12–38)</td>
<td>21 (11–38)</td>
<td>20 (12–38.3)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

CCU, cardiac care unit; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAG, coronary artery angiography; ADHF, acute decompensated heart failure.

Association of biomarkers with the MACEs

Fig. 3 represents each blood biomarker measured at CCU discharge. Only the NGAL and cystatin C were significantly higher in the MACE group than in the non-MACE group. The urinary biomarkers of albumin, NAG, and L-FABP were not significantly different between these two groups (data not shown). Multivariate logistic analysis demonstrated that the plasma NGAL, length of CCU stay, and existing diabetes mellitus and ADHF were independent risk factors for MACEs after CCU discharge (Table 2). Among the biomarkers measured at CCU discharge, the ROC analysis revealed that only the plasma NGAL could predict MACEs within 6 months after CCU discharge with statistical significance (Table 3).

![Fig. 1. Study flow chart. CCU, cardiac care unit; MACE, major adverse cardiac event; RRT, renal replacement therapy.](image1)

![Fig. 2. Comparison of the neutrophil gelatinase-associated lipocalin (NGAL) at cardiac care unit discharge between patients with or without worsening renal function (WRF) during hospitalization. The NGAL value was significantly higher in patients with WRF than those without WRF (NGAL: 295.1 ± 281.7 ng/mL vs. 194.6 ± 198.7 ng/mL, respectively; p = 0.014).](image2)

![Fig. 3.](image3)
Fig. 3. Comparison of the blood biomarkers at cardiac care unit discharge between the major adverse cardiac event (MACE) group and the non-MACE group. The neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C were significantly higher in the MACE group than in the non-MACE group (NGAL: 332.8 ± 327.7 ng/mL vs. 173.1 ± 136.8 ng/mL, respectively, p = 0.005; cystatin C: 1.28 ± 0.64 mg/L vs. 1.08 ± 0.54 mg/L, p = 0.030). NT pro-BNP, N-terminal pro-brain natriuretic peptide; BNP, brain natriuretic peptide; Cre, creatinine.

Table 2
Multivariate logistic regression analysis for MACE.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β coefficient</th>
<th>SE</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL (ng/mL)</td>
<td>0.0036</td>
<td>0.0015</td>
<td>1.0036 (1.0008–1.0071)</td>
</tr>
<tr>
<td>CCU stay (d)</td>
<td>−0.092</td>
<td>0.050</td>
<td>0.91 (0.80–0.98)</td>
</tr>
<tr>
<td>DM</td>
<td>0.68</td>
<td>0.27</td>
<td>3.86 (1.36–11.6)</td>
</tr>
<tr>
<td>ADHF</td>
<td>0.64</td>
<td>0.26</td>
<td>3.62 (1.32–10.5)</td>
</tr>
</tbody>
</table>

SE, standard error; CI, confidence interval; NGAL, neutrophil gelatinase-associated lipocalin; CCU, cardiac care unit; DM, diabetes mellitus; ADHF, acute decompensated heart failure.

Table 3
The receiver operating characteristics analysis for predicting MACE.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cut-off</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL</td>
<td>90.1 ng/mL</td>
<td>0.669</td>
<td>0.541–0.763</td>
</tr>
<tr>
<td>NT-pro BNP</td>
<td>5130 pg/mL</td>
<td>0.607</td>
<td>0.463–0.712</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.18 mg/dL</td>
<td>0.590</td>
<td>0.431–0.768</td>
</tr>
<tr>
<td>BNP</td>
<td>414.6 pg/mL</td>
<td>0.571</td>
<td>0.427–0.762</td>
</tr>
<tr>
<td>Cystatin C</td>
<td>0.87 mg/L</td>
<td>0.634</td>
<td>0.499–0.734</td>
</tr>
<tr>
<td>Urinary albumin</td>
<td>47.5 mg/g Cre</td>
<td>0.592</td>
<td>0.441–0.695</td>
</tr>
<tr>
<td>Urinary NAG</td>
<td>12.91 μg/g Cre</td>
<td>0.554</td>
<td>0.435–0.674</td>
</tr>
<tr>
<td>Urinary L-FABP</td>
<td>202.3 μg/g Cre</td>
<td>0.580</td>
<td>0.412–0.692</td>
</tr>
</tbody>
</table>

NGAL, neutrophil gelatinase-associated lipocalin; NT-pro BNP, N-terminal pro-brain natriuretic peptide; Cre, creatinine; NAG, N-acetyl-β-D-glucosaminidase; L-FABP, L-type fatty acid-binding protein; AUC, area under the curve; CI, confidence interval.
Combination of NGAL and BNP for predicting MACE

To evaluate the association of plasma NGAL with the time-dependent MACE-free rate, the enrolled patients were classified into three groups: the high NGAL (>75th percentile) group, mid NGAL (interquartile) group, and low NGAL (<25th percentile) group. Fig. 4 shows the Kaplan–Meier curve analysis of MACE-free patients divided by the plasma NGAL at CCU discharge. Higher NGAL levels at discharge were significantly associated with a worse outcome. The Cox proportional hazard model showed that the hazard ratio of the high NGAL group (>250 ng/mL) to the low NGAL group (<100 ng/mL) was 5.14 (95% confidence interval [CI] 1.84–18.2, p < 0.01). For a more effective prediction of the MACEs, a combination analysis of NGAL and BNP was performed. Firstly, the area under the curve (AUC) of the ROC curve for the combination value of the prediction of MACEs was higher than that of NGAL or BNP alone, but this difference did not reach statistical significance (AUC = 0.675, 95% CI: 0.558–0.774). To demonstrate the additional effect of BNP, we compared the MACE-free rate specified by the combination of NGAL and BNP to that by NGAL alone (Fig. 5). Patients with a higher value of NGAL and BNP above the cut-off points (NGAL >90.1 ng/mL and BNP >414.6 pg/mL) had a lower MACE-free rate than those with a high value of NGAL alone (p = 0.03). Next, we stratified the patients in four groups using the cut-off value acquired in the ROC analysis: (1) high BNP and high NGAL; (2) high BNP and low NGAL; (3) low BNP and high NGAL; and (4) low BNP and low NGAL. Then the MACE-free rate was plotted in the Kaplan–Meier manner, and each group was compared. Fig. 6 shows the cumulative event-free rate curve of patients divided by the NGAL and BNP levels at CCU discharge. When the NGAL and BNP were higher than the cut-off values, the incidence of the MACEs significantly increased. The hazard ratio was 3.05 (95% CI 1.51–5.96, p < 0.01).

Discussion

The present study demonstrated that the plasma NGAL measured at CCU discharge can predict MACEs in a heterogeneous cohort of critically ill cardiac patients. In addition, the combination of NGAL and BNP at CCU discharge provided a distinct prognostic stratification. Our study was clinically relevant for a couple of reasons. Firstly, it enrolled a wide variety of patients with cardiac...
diseases, including those with ACS and ADHF. Secondly, the plasma NGAL was measured at CCU discharge when the patients responded to the treatment and were in stable conditions.

WRF is one of the strongest risk factors for decompensated heart failure [28]. The negative impacts by renal injury on the outcomes of cardiac diseases have been recognized as a part of the cardio-renal syndrome [3]. Critically ill cardiac patients are frequently exposed to different potential renal insults such as contrast media injection, infection, low output, and systemic congestion. Although WRF is often defined by serum creatinine elevation, recent development of new AKI biomarkers that can detect AKI more sensitively than serum creatinine enable clinicians to monitor renal injury more timely and accurately. Therefore, several clinical studies evaluated the performance of new AKI biomarkers in cohorts of cardiac patients. In this study, although the complication of WRF did not significantly differ in patients with or without MACE, NGAL levels at CCU discharge could not only predict the MACE but also respond to WRF. Thus, these data suggested that NGAL levels have better prediction for MACE than WRF complication.

Chen and colleagues reported the association of AKI biomarkers measured at CCU admissions with poor clinical outcomes at 6-month follow-up [29]. They demonstrated that urinary NGAL and serum interleukin (IL)-18 can predict the mortality of CCU patients, whereas serum cystatin C had the best discriminative value for predicting AKIs. Alvelos and colleagues reported that the serum NGAL measured at admission had a significant prognostic predictive value in acute heart failure [21]. Other studies evaluated the role of NGAL in coronary heart disease patients. For example, Lindberg and colleagues showed that a high plasma NGAL on admission independently predicted all-cause mortality and MACEs within 2 years after primary PCI in ST-segment elevation myocardial infarction patients [18]. Zografos and colleagues reported that the NGAL levels were higher in patients with stable coronary heart disease than in those with normal coronary arteries evaluated by elective angiography [30].

Only one clinical study examined the performance of NGAL measured at discharge. Maisel and colleagues reported that the plasma NGAL at hospital discharge was a strong prognostic indicator of 30-day outcomes for patients admitted for acute heart failure [16]. Although the biomarker measurement at CCU admission is expected to reflect the severity of illness and to predict the short-term outcomes, the measurement at discharge may provide more clinically relevant significance. It appears logical to assess the NGAL levels at discharge, because the circulatory dynamics were relatively stable, and many other parameters were almost uniformly conditioned by hospital discharge. However, the LVEF data were only measured at CCU admission, because we think that measuring that at admission reflects the severity of acute injury to the heart better than at any other time point. In addition, improvement in LVEF may require a longer time than the length of CCU stay. For these reasons, LVEF was evaluated at admission. Predicting the long-term outcomes of patients who have recovered from acute critical conditions can provide additional advantages for patient management, including close monitoring and intensive medication. In the present study, we measured biomarkers at discharge from CCU and found a significant association with the NGAL and poor outcomes after discharge. Therefore, the higher NGAL group should be closely followed after discharge, and heart and kidney protective medications, including diuretics, renin-angiotensin system inhibitors, and inotropic agents, should be adjusted carefully.

Although the BNP was considered to be standard for the risk prediction of heart failure [31,32], the measurement of the NGAL was a powerful predictor for MACEs as well as BNP in patients with heart failure [16]. Because patients admitted to the CCU have diverse backgrounds (e.g., ischemic heart disease, cardiomyopathy, aortic disease, and pulmonary embolism), using a combination of the NGAL and BNP for risk stratification was beneficial in real clinical practice. While BNP is a marker of ventricular stretch and therefore a marker of volume overload, NGAL is a marker of renal tubular injury. Thus, using a combination of these markers may not only predict cardiac events, but also predict cardiac-renal hemodynamic events in CCU patients. Although BNP did not show any significant association with MACEs in the present cohort, this biomarker is widely used for evaluating heart failure. A recent clinical study conducted by Maisel and colleagues reported on a significant predictor of MACEs by using a combination of NGAL and BNP in a cohort of ADHF (not including ischemic heart disease) [16]. Similarly, evaluating a combination of NGAL and BNP may provide clinically relevant information for the predictive value of MACEs in this cohort.

Why can the AKI biomarker, NGAL, predict the outcomes of cardiac patients? First, the remote organ is affected by renal injury, which is recognized as cardio-renal syndrome, and appears to account for the good outcome prediction by the NGAL in cardiac patients. Second, several studies suggest the possible role of the NGAL in heart diseases. Yokested and colleagues demonstrated the cardiac NGAL expression by using a rat myocardial infarction model and human heart failure tissue [33]. The NGAL co-localized with metalloproteinase-9 and stabilized its protease activity in infarcted hearts and atherosclerotic plaques, suggesting that the NGAL causes plaque instability [34]. Thus, the NGAL may have a strong relation with active vascular remodeling itself and may also reflect the severity of cardiovascular disease, in addition to renal tubular injury.

Reportedly, the plasma NGAL was increased by sepsis and was significantly higher in septic AKI patients than in other AKI patients and non-AKI patients [35–37]. These results indicated that the plasma NGAL reflects systemic leukocyte activation. In critically ill cardiac patients treated in the CCU, systemic inflammation caused by sepsis, pneumonia, device-related infection, and endocarditis are frequently observed. As previously described, the NGAL has strong implications in multiple settings of acute critical illness of AKI, heart failure, coronary heart disease, and systemic inflammation. These wide spectrums, including the extra-renal aspects of
the NGAL, enable it to predict the outcomes of heterogeneous patients as well.

**Study limitations**

There are several limitations that may affect the results of our study. First, it was conducted at a single hospital, and the sample size (n = 127) was small. Evaluations in multicenter CCUs with larger cohorts should be conducted to validate our findings further. Second, we collected only one point of markers. The comparison of data with that of admission or sequential measurement of markers will provide more superior insight on the risk stratification. Third, other AKI biomarkers, such as urinary IL-18 and KIM-1, which were reported to be useful in cardiac patients [38,39], were not measured in the present study. Fourth, definition of MACE included the revascularization and emergent readmission in this study. Further study with more stringent endpoints (e.g. only hard-endpoints) is necessary to confirm the obtained results in this study, although a larger sample size will be required. Fifth, revascularization rate was high (approximately 20%) in our cohort. The enrolled patients frequently had multi-vessel disease and were usually complicated with heart failure because patients with stable angina or pharmacologically controlled unstable angina were not admitted to our CCU. Therefore, we did not include elective PCI for MACE. We basically treated only the culprit lesions in these patients, however another revascularization was often required to prevent the progression of heart failure in the additional unexpected hospitalization. This unstable clinical status might explain a high revascularization rate in this cohort. Finally, although baseline serum creatinine should impact the diagnosis of WRF and AKI by definition, no standardized criteria have been suggested to date. Recent clinical studies evaluated the impact of different definitions of baseline serum creatinine on the AKI diagnosis and severity [40,41]. In addition, the serum creatinine at CCU admission and discharge seemed to not be proper baseline values. Some patients showed increased serum creatinine concentrations at CCU admission, while others had a persistent elevation in the serum creatinine concentrations until CCU discharge compared to the outpatient measurements. Therefore, we defined the baseline serum creatinine as the minimal value for each patient.

In conclusion, our study demonstrated that the plasma NGAL at discharge can be a significant predictor for prognosis among patients in the CCU. Furthermore, a combination of the NGAL and BNP provides a remarkably accurate prediction of adverse events. The measurement of the NGAL at discharge may enable us to identify the high-risk patients and to adjust the management of the patients. Further study is expected to confirm the predictive power of the NGAL in cardiovascular diseases.

**Funding**

This study was supported by Grants-in-Aid #17H05929 (to YH), Core Research for Evolutional Science and Technology from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and the Tokyo Society of Medical Sciences (KD).

**Conflict of interest**

The authors declare that there is no conflict of interest.

**Acknowledgments**

We have presented this study at the 61st Annual Scientific Session of the Japanese College of Cardiology (2013, Kumamoto, Japan). We acknowledge Alere Medical Inc. (Tokyo, Japan) for its partial support in the collection and testing of blood samples for this study.

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.jcc.2015.05.010.

**References**
