Journal of Cardiology 67 (2016) 184–191

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

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
Received in revised form 15 May 2015
Accepted 19 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.

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

Abbreviations: NGAL, neutrophil gelatinase-associated lipocalin; AKI, acute kidney injury; CCU, cardiac care unit; MACEs, major adverse cardiac events; WRF, worsening renal function; PCI, percutaneous coronary intervention; L-FABP, L-type fatty acid-binding protein; KIM-1, kidney injury molecule-1; ADHF, acute decompensated heart failure; ACS, acute coronary syndrome; NT-proBNP, N-terminal pro-brain natriuretic peptide; NAG, *N*-acetyl-β-D-glucosaminidase; eGFR, estimated glomerular filtration rate; ROC, reciever operating characteristics.

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http://dx.doi.org/10.1016/j.jjcc.2015.05.010
0914-5087/

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 injury 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 m^2), 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 χ^2 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.