Journal of Critical Care 34 (2016) 89–94

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Neutrophil gelatinase-associated lipocalin levels during the first 48 hours of intensive care may indicate upcoming acute kidney injury

Fatih Kamis [a], Itir Yegenaga [a,*], Mert Musul [b], Canan Baydemir [c], Sibel Bek [a], Betül Kalender [a], Nur Baykara [d]

[a] Department of Internal Medicine, Kocaeli University Medical School, University Hospital, Umuttepe Campus, Uctepeler, Kocaeli, Turkey
[b] Department of Biochemistry, Kocaeli University Medical School, University Hospital, Umuttepe Campus, Uctepeler, Kocaeli, Turkey
[c] Department of Biostatistics, University Hospital, Umuttepe Campus-Uctepeler, Kocaeli University Medical School, Kocaeli, Turkey
[d] Department of Intensive Care, University Hospital, Umuttepe Campus-Uctepeler, Kocaeli University Medical School, Kocaeli, Turkey

ARTICLE INFO

Available online xxxx
Keywords:
Acute kidney injury
Critically ill
Biomarker
NGAL

ABSTRACT

Purpose: The recognition of acute kidney injury (AKI) as early as possible is important in the intensive care unit. This study proposes that serum and urine levels of neutrophil gelatinase-associated lipocalin (NGAL) may be used for this purpose.
Methods: One hundred and seven critically ill adult patients with no previous renal failure were included. NGAL levels were measured during the first 48 hours after admission; NGAL levels were followed for 7 days and classified based on Risk, Injury, Failure, Loss, and End-Stage Renal Failure criteria.
Results: The AKI incidence was 35.5%, and serum NGAL (sNGAL) and urinary NGAL (uNGAL) levels were higher in the AKI group. The area under the receiver operating characteristic curve was 0.76 ($P < .001$) for sNGAL and 0.75 ($P < .001$) for uNGAL. Seventy-one percent of AKI cases were observed within 48 hours, with 11 additional cases in the ensuing 7 days. The mean serum creatinine levels in the 11 patients were not different from non-AKI levels ($P = .197$), but the NGAL values were different, and the area under the receiver operating characteristic curve for sNGAL uNGAL was 1.00 ($P = .014$) and 0.93 ($P = .02$), respectively.
Conclusions: Most AKI cases were diagnosed within the first 48 hours after admission, and NGAL was useful for predicting upcoming AKI.

1. Introduction

Acute kidney injury (AKI) is a frequent and severe complication observed in patients in the intensive care unit (ICU) [1–2], and kidney injuries in ICU patients may affect remote organs and lead to multiorgan failure, which may be difficult to treat. AKI development in the ICU is related to higher mortality (50%-70%) and morbidity rates [2] as well as increased risk for chronic renal failure and long-term maintenance renal replacement therapy (RRT) after discharge [3]. Therefore, it is important to determine which patients are at a high risk for AKI in the ICU and to treat them as early as possible [4]. Many recent investigations have aimed at identifying biomarkers for AKI diagnosis before increases in serum creatinine for use in a manner similar to troponin I, which has been successfully used for many years to predict acute myocardial infarction [5].

To date, AKI diagnosis has been limited to observations of increasing levels of serum creatinine, decreases in urine output, and alterations in urinary chemistry [6–7]. Nevertheless, serum creatinine levels do not increase significantly until renal function has decreased to 50%; in addition, the level of serum creatinine may be affected by the patient's muscle mass, catabolic state, protein intake, weight, sex, and tubular secretion of creatinine [8–9]. Therefore, applying serum creatinine as a biomarker for diagnosing AKI may result in the loss of valuable time. Despite recent advancements in our understanding of the molecular mechanisms underlying AKI, the application of such improvements to the bedside has not been as efficient as expected. This finding is not unexpected because AKI is a complicated condition and develops as a result of many different etiologic factors. In addition, interventions may be delayed because of the lack of an appropriate biomarker for obtaining a timely diagnosis of AKI [4].

Ideal biomarkers for the sensitive, early, and specific detection of AKI should be noninvasive and involve the rapid utilization of urine or blood samples in a clinical laboratory. These biomarkers should also be related to the subtype and pathogenesis of AKI. Several biomarkers have recently been recommended for this purpose [4]. Neutrophil gelatinase-associated lipocalin (NGAL) is one of the earliest proteins expressed in the kidney after ischemic or toxic injury [4]. It has been reported that serum (sNGAL) and urine (uNGAL) NGAL values might indicate AKI

* Corresponding author at: Uctepeler, Umuttepe Campus, Kocaeli University Medical School, University Hospital, Department of Internal Medicine, 41380 Izmit, Kocaeli, Turkey. Tel.: +90 2623037523; fax: +90 2623037001.
E-mail addresses: fatihkamis@hotmail.com (F. Kamis), itiryegenaga@hotmail.com (I. Yegenaga), mertmusul@hotmail.com (M. Musul), canandoruk@hotmail.com (C. Baydemir), baykaranur@yahoo.com (N. Baykara).

http://dx.doi.org/10.1016/j.jcrc.2016.04.012
0883-9441/

development before increases in serum creatinine, especially in patients whose AKI-causing insult was certain. Nonetheless, it remains unclear whether this finding also applies to AKI development in complicated ICU patients [4,9]. Accordingly, this study was designed to test the reliability of using the sNGAL and uNGAL values of critically ill patients in the first 48 hours after ICU admission for estimating the development of upcoming AKI.

2. Materials and methods

Patients older than 17 years, without known chronic kidney disease, RRT, or previous kidney transplant, who were admitted to the combined ICU (medical and surgical) for more than 48 hours were prospectively included in this study (Fig. 1). The demographic features; medical history; and clinical, biochemical, and hematological parameters of the patients were prospectively recorded. The patients' clinical and laboratory data were collected for 7 days or until death or discharge from the ICU. Primary hepatic failure and diabetes mellitus were defined based on a medical history of cirrhosis and the use of antidiabetic drugs, respectively. The presence of chronic obstructive pulmonary disease was accepted if the patients needed bronchodilators. Cardiovascular disease was defined as cardiomyopathy, ischemic heart disease, or peripheral arterial disease [10]. Sepsis and systemic inflammatory response syndrome (SIRS) were defined based on criteria determined by the American College of Chest Physicians and the Society of Critical Care Medicine [11–12]. During the first 24 hours, the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scoring systems were used to assess the severity of the cases [13,14]. AKI was diagnosed based on Risk, Injury, Failure, Loss, and End-Stage Renal Disease (RIFLE) criteria upon admission and during the next 7 days in the ICU [6–7,15]. If the baseline serum creatinine value was not available, the lowest creatinine value over the previous 3 months was used [6]. In this study, the sNGAL and uNGAL levels were measured within 48 hours after admission because it was not convenient to assess the NGAL levels of each patient admitted to the ICU and it was not practical to perform a sequential assessment to determine the time of AKI development if the time of insult was unknown. For these reasons, from a practical point of view, an ICU stay length of 48 hours was selected for determining NGAL values.

Blood and urine samples were obtained within 48 hours after admission. The blood samples were centrifuged for 10 minutes, and the serum was then separated and stored at −80°C until determination of NGAL levels by micro-ELISA (BioVendor R&D).

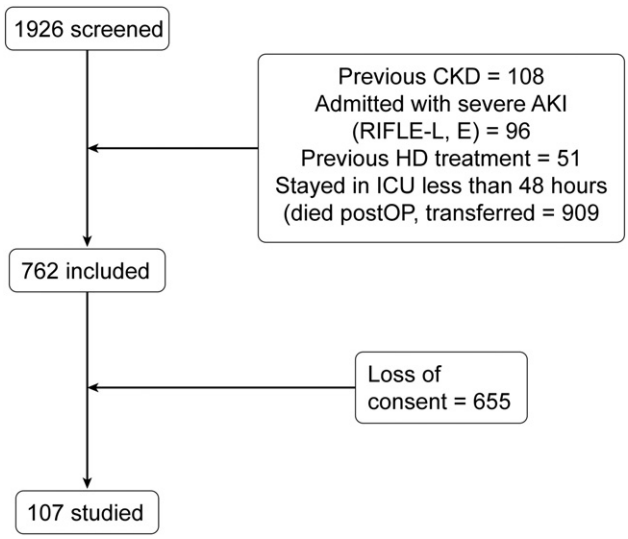

Fig. 1. Flowchart of the patients assessed for inclusion in this study.

Every participant or their next of kin provided written informed consent after they were clearly informed of the study details. This study was approved by the Kocaeli University Ethical Committee (2011/39-14/3).

2.1. Statistical analysis

Statistical analyses were performed using IBM SPSS 20.0 (SPSS Inc, Chicago, IL). Continuous variables were compared between the 2 groups using Student *t* test, and categorical variables were compared using χ^2 test. The distribution of the variables was tested by the Kolmogorov-Smirnov test; if the distribution was not normal, the Mann-Whitney *U*, Kruskal-Wallis one-way variance analysis, and Tukey multiple-comparison tests were applied. Pearson, Fisher exact, and χ^2 tests were used for analyzing categorical variables. The numerical variables are presented as the means ± standard deviation, medians (25th percentile-75th percentile), or frequencies (%). Receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC), including the 95% confidence interval (CI), was calculated. The AUC values were compared using nonparametric tests, and the

Table 1
Main clinical and laboratory features of the patients

	RIFLE (+) (n = 38) n (%) or median (25%-75%)	RIFLE (−) (n = 69) n (%) or median (25%-75%)	*P*
Male	14 (36.8)	34 (49. 3)	.528
Age	66.0 (53.0-75.0)	61.0 (42.0-71.0)	.231
BMI	26.7 (24.1-28.4)	25.3 (22.3-28.3)	.150
Admission			
Medical	16 (42.1)	41 (59.4)	.086
Surgical	22 (57.9)	28 (40.6)	.086
Emerg. surgery	13 (34.2)	20 (29.0)	.361
Primary diagnosis			
Trauma	6 (15.8)	10 (14.5)	.033
CNS	6 (15.8)	27 (39.1)	
Pulmonary	9 (23.7)	20 (29)	
GIS	14 (36.8)	10 (14.5)	
GUS	2 (5.3)	1 (1.4)	
Hematologic	0 (0)	1 (1.4)	
CVS	1 (2.6)	0 (0)	
Nephrotoxic agents			
Contrast	15 (39.5)	23 (33.3)	.367
Aminoglycosides	1 (2.6)	0 (0)	
Comorbidity			
Immunosuppression	9 (23.7)	18 (26.1)	.784
Hypertension	16 (42.1)	24 (34.8)	.454
Diabetes mellitus	9 (23.7)	12 (17.4)	.433
Liver failure	1 (2.6)	1 (1.4)	.666
Coronary artery disease	11 (28.9)	16 (23.2)	.512
SIRS	34 (89.5)	52 (75.4)	.079
Sepsis	17 (44.7)	27 (39.1)	.573
APACHE II	28.00 (21.00-30.20)	21.00 (16.50-25.50)	.001
SOFA	8.00 (6.00-11.00)	5.00 (4.00-7.0 0)	.001
MAP (mm Hg)	70.00 (55.00-78.50)	76.00 (66.00-83.00)	.016
Ventilated	33 (86.8)	57 (82.6)	.566
Glucose (mg/dL)	140.5 (106.25-184.25)	148.00 (114.50-194.00)	.526
Urea (mg/dL)	83.35 (48.65-126.67)	38.00 (28.00-61.00)	.001
Creatinine (mg/dL)	1.78 (1.05-2.63)	0.70 (0.59-0.85)	.001
NGAL serum (ng/dL)	118.87 (91.55-154.88)	75.72 (53.53-91.95)	.001
NGAL urine (ng/dL)	60.35 (23.55-69.24)	18.00 (9.10-40.09)	.001
Vasopressor	23 (73.7)	17 (24.6)	.001
Albumin	25 (65.8)	18 (26,1)	.001
Colloid	29 (76.3)	37 (53.6)	.021
Furosemide	30 (78.9)	51 (73.9)	.561
Transfusions	27 (71.1)	30 (43.5)	.006
LOS (d)	67 (27-106)	17 (5-28)	.016
Dialysis	8 (21.1)	6 (8.7)	.070
Dead			
Intensive care	23 (60.5)	17 (24.6)	.001
Hospital	25 (65.8)	22 (31.9)	.001

BMI, body mass index; CNS, central nervous system; GIS, gastrointestinal system; GUS, genitourinary system; CVS, cardiovascular system; SIRS, systemic inflammatory response syndrome; MAP, mean arterial pressure; LOS, length of hospital stay.