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## CLINICAL STUDY

# Urine neutrophil gelatinase-associated lipocalin levels predict acute kidney injury in acute decompensated heart failure patients

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## Abstract

**Background:** Acute heart failure (HF) syndromes are frequently complicated with cardiorenal syndromes. The aim of this study was to evaluate the performance of admission neutrophil gelatinase associated lipocalin (NGAL) levels to predict diuretic dose requirement and to predict the occurrence of acute kidney injury (AKI) in patients presenting with acute decompensated HF. **Methods:** Patients admitted with HF symptoms between December 2010 and October 2011 were prospectively enrolled. Samples were obtained for NGAL and brain natriuretic peptide. Patients were followed up until discharge or for three days, whichever happened first. They were grouped either to have AKI according to "Acute Kidney Injury Network" criteria or not ("no-AKI"). **Results:** One hundred patients were enrolled. Urine NGAL levels were higher in AKI group (median 31.3 vs. 16.2 ng/mL) ( $p < 0.001$ ). Oral furosemide using rates on admission was 60.5% in AKI group, 31.6% in no-AKI group. More AKI developed in patients using less furosemide orally on admission ( $p = 0.023$ ). Although the mean furosemide doses were similar on the first day (80 mg), diuretic dose increment was less on the following days in AKI group. Urine NGAL levels with 12 ng/mL cut-off value had sensitivity of 79% and specificity of 67% for predicting AKI. Multiple logistic regression analysis yielded an odds ratio of 10.9 for NGAL levels to predict AKI. **Conclusion:** Urine NGAL level in decompensated HF patients was not a significant predictor of diuretic dose requirement, but was a good marker for predicting AKI at 12 ng/mL cut-off value.

## Keywords

Acute kidney injury, cardiorenal syndrome, diuretic, heart failure, neutrophil gelatinase associated lipocalin

## History

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## Introduction

Although heart failure (HF) is a chronic disease, most patients with HF experience acute attacks of decompensation, namely acute heart failure syndromes (AHFS).<sup>1</sup> Cardiorenal syndromes (CRSs) may complicate the AHFS when acute kidney injury (AKI) ensues resulting in an increased rate of mortality, complications and length of hospital stay.<sup>2,3</sup> Renal function may improve after diuretic treatment in some of the patients with AHFS as with the regressing congestion.<sup>4</sup>

Neutrophil gelatinase associated lipocalin (NGAL) is one of the promising markers that can assist in early recognition of AKI.<sup>5,6</sup> It can be measured in plasma and urine. Urine NGAL can be advantageous and easier to measure since it is easily obtained, stable, specific and not affected from urine neutrophils. Hypovolemia and diuretics do not affect the levels of urinary NGAL, thus can be used to differentiate AKI and prerenal azotemia.<sup>7</sup> In stable HF patients, it was shown that decreases in GFR and increases in N-terminal probrain natriuretic peptide (NT-proBNP) were associated with

elevations in NGAL.<sup>8</sup> The pathophysiological association between HF and declining renal functions can evolve into a more complex situation in patients receiving diuretics. Diuretics are generally used on the basis of clinical guidance, but usually without a guidance of a laboratory parameter. NGAL is thought to be the missing link in the triangle of kidney–heart–inflammation, so it might be used as an early marker to develop algorithms that will guide diuretic treatment for patients with AHFS who are at risk of AKI.<sup>9</sup>

The primary aim of this study was to evaluate the performance of urine NGAL in predicting the occurrence of AKI in AHFS patients. The secondary aim was to test the hypothesis that urine NGAL at admission could predict the dose of intravenous furosemide required to relieve the symptoms of AHFS.

## Material and methods

### Study population

Adult patients who were admitted to the emergency room of a University Hospital with acute decompensated HF between December 2010 and October 2011, and who consented were prospectively enrolled. This study was approved by Institutional Ethics Board and supported by the Turkish

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Acute HF was diagnosed clinically. Congestive HF signs and symptoms (dyspnea, orthopnea, paroxysmal nocturnal dyspnea, decreased exercise capacity) and hypervolemia signs (rales, jugular venous distension, peripheral edema) on physical examination were evaluated as well as the underlying chronic conditions and the acute conditions that might have led to the decompensation of the chronic heart disease.

Patients with chronic renal replacement treatment, congenital heart disease, contrast nephropathy and urinary infection were excluded. Demographic characteristics, chronic diseases, medications, complaints and physical findings, NYHA functional class, laboratory tests and imaging results were recorded for the first three days of admission when available. Patients were followed up until death or discharge from the hospital to determine the length of hospital stay and the mortality rate.

### Laboratory assessment

Serum BNP levels were routinely ordered in patients with dyspnea and presumptive or confirmed diagnosis of HF in the emergency room. Urine samples for NGAL were obtained on admission. Urine samples were centrifuged at 1500 rpm for 15 min, and were kept until they were collectively analyzed. Physicians taking care of the study patients were not informed about the results of NGAL and there was no intervention to the treatment protocol.

Plasma BNP was determined by using microparticle enzyme immunoassay method with AxSym device (AxSym System BNP Reagent Pack, Abbott Laboratories, Abbott Park, IL). Values > 100 pg/mL were accepted as positive.

Urine NGAL was determined by using Enzyme-Linked Immuno Sorbent Assay (ELISA) kit (BioVendor Research and Diagnostic Products, Modrice, Czech Republic) with Sirio ELISA reader (Seac, Radim, Italy).

### Definitions

For AKI definition, “Acute Kidney Injury Network” (AKIN) criteria were used.<sup>10</sup> The difference between the highest creatinine in 48–72 h of admission and basal creatinine was calculated. Creatinine difference  $\geq 0.3$  mg/dL was defined as AKI. Chronic kidney disease was defined as permanent and steady kidney disease for at least three months (estimated GFR (eGFR) < 60 mL/min and creatinine variability < 25%). Glomerular filtration rate was calculated using the eGFR using modification of diet in renal disease formula (eGFR =  $186 \times \text{serum creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.210 \text{ if black}] \times [0.742 \text{ if female}]$ ). For patients who did not have previous serum creatinine values, stable low eGFR values during hospital stay were considered as chronic kidney disease.

### Statistical analysis

Data were entered to Statistical Package for the Social Sciences (SPSS)-15 program (Chicago, IL). Means, standard deviations and parametric tests were used when data were normally distributed, medians and non-parametric tests were used if the data were not normally distributed.

The relationship between patients' outcomes and NGAL values was evaluated using logistic regression analysis to control for confounding factors. Cut-off value for urinary NGAL was defined by using receiver operating characteristic (ROC) analysis. The relationship between BNP levels and congestive HF was evaluated with Pearson chi-square and Fisher's exact tests.  $p$ -Value < 0.05 was defined as statistically significant.

### Results

One hundred patients were enrolled in the study. Mean age of the patients was  $70.9 \pm 12.0$  and 49% of them were male (Table 1). Most frequent admission complaint was dyspnea (92%) and hypertension was the most prevalent chronic disease (81%). Fifty-five percent of the patients were using per oral furosemide on admission. There were no differences between the AKI and non-AKI groups in terms of admission median systolic blood pressure (135 vs. 130 mmHg), median

Table 1. Demographic characteristics, known chronic diseases and drug usage for AKI and no AKI groups at the time of admission.

Variable	AKI ( <i>n</i> = 19)	No AKI ( <i>n</i> = 81)	<i>p</i> Value
Age (mean $\pm$ SD, years)	76.1 $\pm$ 12.7	69.7 $\pm$ 11.6	>0.05
Male	57.9%	46.9%	>0.05
Chronic diseases	<i>n</i> (%)	<i>n</i> (%)	>0.05
Hypertension	13 (68.4)	58 (71.6)	>0.05
Congestive heart failure	11 (57.9)	54 (66.7)	>0.05
Coronary heart disease	14 (73.6)	47 (58)	>0.05
Diabetes mellitus	6 (31.6)	31 (38.3)	>0.05
Chronic obstructive lung disease	6 (31.6)	25 (30.8)	>0.05
Atrial fibrillation	6 (31.6)	22 (27.1)	>0.05
Chronic kidney disease	12 (63.2)	19 (23.5)	0.003
Asthma	1 (5.2)	8 (9.8)	>0.05
Others <sup>a</sup>	18 (94.7)	64 (79)	>0.05
Drugs on admission			
Furosemide	6 (31.6)	49 (60.5)	0.023
ACEI/ARB	8 (42.1)	37 (45.7)	>0.05
Beta blocker	10 (52.6)	32 (39.5)	>0.05
Digoxin	7 (36.8)	27 (33.3)	>0.05
Inhaler treatment	4 (21.1)	22 (27.1)	>0.05
Antiplatelet drugs	13 (68.4)	57 (70.4)	>0.05
Calcium channel blockers	5 (26.3)	19 (23.5)	>0.05
Thiazide	4 (21.1)	18 (22.2)	>0.05
Statin	4 (21.1)	15 (18.5)	>0.05
Insulin	4 (21.1)	13 (16)	>0.05
Spironolactone	1 (5.3)	11 (13.6)	>0.05
Metformin	1 (5.3)	11 (13.6)	>0.05
Oral antidiabetics other than metformin	2 (10.5)	10 (12.3)	>0.05
Alpha blocker	2 (10.5)	8 (9.9)	>0.05
Others <sup>b</sup>	11 (57.9)	67 (82.7)	>0.05

Notes: AKI, acute kidney injury; SD, standard deviation; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. One patient may have more than one comorbidity. One patient may use more than one drug on admission.

<sup>a</sup>Heart valve disease, collagen vascular disease, cerebrovascular accident, malignancy, hyperlipidemia, benign prostate hypertrophy, hypothyroidism, hyperthyroidism, familial Mediterranean fever, varices, pulmonary thromboembolism, depression, epilepsy, gout, ulcerative colitis, osteoporosis, osteoarthritis, bronchitis, parkinsonism, chronic hepatitis C.

<sup>b</sup>Nitrate, proton pump inhibitor, corticosteroid, colchicine, amiodarone, strontium, enoxaparin, levothyroxine, alendronate, allopurinol, theophylline, mycophenolate mofetil, cyclophosphamide, ivabradine, leflunomide, cyclosporine, gabapentin, azathioprine.

diastolic blood pressure (70 vs. 80 mmHg) and median serum sodium concentration (135 vs. 136 mEq/L), respectively.

AKI developed in 19% of the patients during the first 72 h of the follow-up. Fourteen patients with AKI (73.7%) had an increase of more than 0.3 g/dL in creatinine, while the rest (26.3%) had a decrease in this period. On the other hand, among patients who were in the non-AKI group, 11 patients (13.6%) had some decrease in creatinine but not as much as 0.3 g/dL. The median serum creatinine level of the patients with AKI was 1.56 g/dL on admission, while of the patients in the non-AKI group was 1.01 g/dL.

There was no statistically significant age and gender difference between the patients who developed AKI and who did not. However, patients with AKI had a higher prevalence of underlying chronic kidney disease and lower percentage of per oral furosemide use before admission (Table 1). Community acquired pneumonia was the most common additional comorbidity (25%) in the study cohort. Thirty-five percent of the patients had NYHA class 2, 40% had class 3 and 20% of the patients had class 4 HF. There was no difference between classes with regard to the development of AKI in univariate analysis.

The mean length of hospital stay was  $7.4 \pm 10.7$  days. The length of stay in the hospital was statistically significant for patients who developed AKI when compared to patients who did not develop AKI (Table 2). Hospital mortality was higher among patients with AKI when compared to patients without AKI (Table 2).

Plasma BNP levels were statistically higher in AKI group when compared to those patients without AKI ( $2118 \pm 1130$  vs.  $1379 \pm 1216$  pg/mL, respectively;  $p = 0.009$ ), so were the urine NGAL levels: median urine NGAL level was 31.2 ng/mL in the AKI group and 16.2 ng/mL in non-AKI group ( $p < 0.001$ ) (Figure 1). Median urine NGAL levels were also higher in patients with underlying chronic kidney disease when compared to those without a history of chronic kidney disease (17.7 vs. 5.5 ng/mL, respectively,  $p = 0.021$ ).

The ROC curve obtained by plotting urine NGAL and AKI frequency yielded an area under the curve (AUC) of 0.7789 (95% CI: 0.66–0.90) (Figure 2). A cut-off value of  $\geq 12$  ng/mL for NGAL showed a sensitivity of 79%, specificity of 67% for predicting AKI. On univariate logistic regression analysis, cut-off value of urine NGAL  $\geq 12$  ng/mL had an odds ratio of 8.9 for the development of AKI.

Table 2. Length of stay and outcome.

Variable	All patients (n = 100)	AKI (n = 19)	No AKI (n = 81)	p
Emergency room	n (%)	n (%)	n (%)	
Discharge	63 (63)	8 (42.1)	55 (67.9)	>0.05
Admission to the ward	31 (31)	9 (47.4)	22 (27.2)	
Death	6 (6)	2 (10.5)	4 (4.9)	
Hospital				
Discharge	86 (86)	13 (68.4)	73 (90.1)	0.024
Death	14 (14)	6 (31.6)	8 (9.9)	
Length of stay (days) <sup>a</sup>				
Emergency room	$3.6 \pm 6.3$	$6.6 \pm 12.2$	$2.9 \pm 3.6$	>0.05
Hospital	$7.4 \pm 10.7$	$15.4 \pm 14.9$	$5.6 \pm 8.5$	

Notes: AKI, acute kidney injury. Only statistically significant  $p$ -values ( $p < 0.05$ ) was defined in table.

<sup>a</sup>Mean  $\pm$  standard deviation.

Although the mean intravenous furosemide doses on the first day were similar between groups (80 mg), diuretic dose increment was less on the following days in AKI group (Figure 3). Patients in AKI and no AKI groups were divided into two subgroups according to the first day diuretic doses (as 80 mg or less, and more than 80 mg). When parameters as first day diuretic dose, age, gender, NYHA class, presence of chronic diseases such as diabetes mellitus and chronic kidney disease, and presence of pneumonia were introduced to a multiple logistic regression analysis, odds ratio of urine NGAL levels in predicting AKI was found to be 10.9.

Patients who died had higher NGAL levels when compared to those who were discharged, but the results were not statistically significant (11.5 vs. 7 ng/mL, respectively) ( $p = 0.17$ ). On the other hand, mean BNP levels were significantly higher for patients who died ( $2232 \pm 1512$  pg/mL) when compared to those who were discharged ( $1404 \pm 1147$  pg/mL) ( $p = 0.047$ ). Urine NGAL levels did not predict mortality

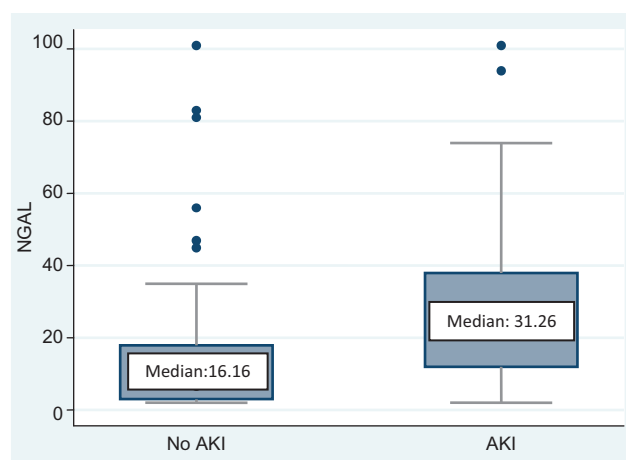


Figure 1. Distribution of urine NGAL (ng/mL) levels and the median NGAL (ng/mL) levels in AKI and no AKI groups. NGAL, neutrophil gelatinase associated lipocalin; AKI, acute kidney injury.

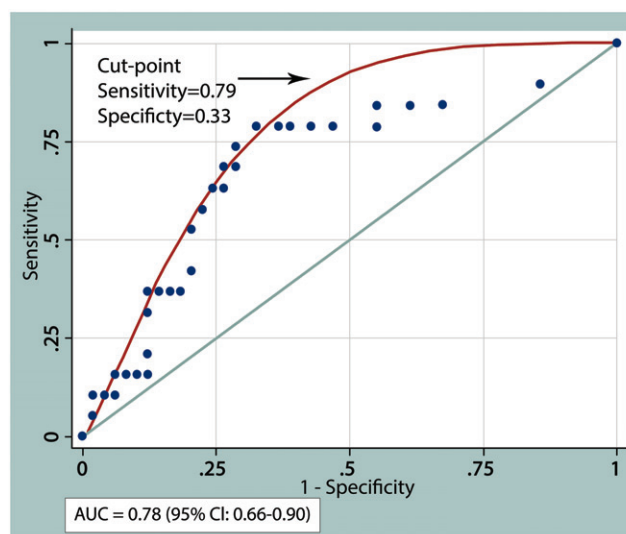


Figure 2. ROC analysis for urine NGAL (ng/mL) levels with regard to presence or absence of AKI. NGAL, neutrophil gelatinase associated lipocalin; AKI, acute kidney injury.



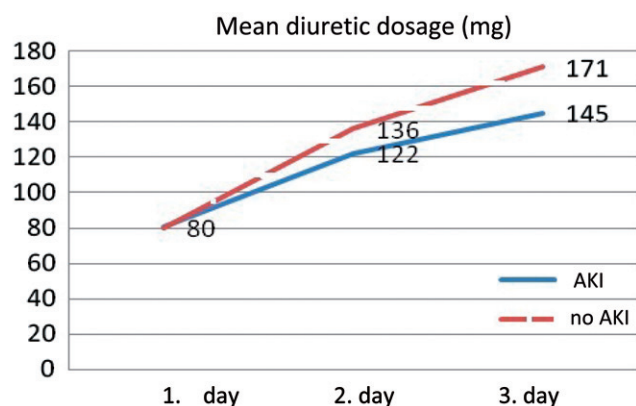


Figure 3. Mean intravenous furosemide doses at the first, second and third day of hospitalization for AKI and no AKI groups. AKI, acute kidney injury.

( $p = 0.17$ ), while BNP levels had statistically significant association with mortality ( $p = 0.047$ ).

## Discussion

In this cohort of acute decompensated HF patients in the emergency room, the incidence of AKI was 19%. Urine NGAL at a cut-off level of 12 ng/mL had a positive predictive value of 85% and a negative predictive value of 58% to predict AKI. Moreover, multiple logistic regression analysis revealed an odds ratio of 10.9 for NGAL in predicting AKI.

Acute HF syndromes can be complicated with CRSs and AKI frequently develops in acute and critical patients.<sup>11</sup> Renal dysfunction during HF is a bad prognostic sign, so early recognition of AKI and appropriate management are very important.<sup>2,3</sup> Heterogeneous studies yielded AKI prevalences between 20% and 60% on admission, reaching to 70% when all hospitalization period is taken into account.<sup>12–15</sup> Sensitive and early markers of AKI might be used to develop algorithms that will guide the management of these patients. One of the promising markers is NGAL, which has been shown to increase before the serum creatinine increment after a renal insult.<sup>16–18</sup>

The diagnostic and prognostic value of NGAL in different patient groups yielded heterogeneous results in previous studies. Urine NGAL was found to be an early prognostic marker in HF patients with normal GFR levels.<sup>19,20</sup> Though, a few studies question the role of NGAL in predicting the risk of AKI, serum NGAL was used as a marker for AKI, and it was also shown to be associated with a higher risk of AKI at different cut-off levels.<sup>21,22</sup> Acute decompensated HF patients with serum NGAL levels over 167.5 ng/mL had 2.7 times increased mortality and 2.9 times increased hospitalization rates.<sup>23</sup> Alvelos et al. defined a cut-off value of 170 ng/mL for serum NGAL to foresee type 1 CRS with 100% sensitivity and 86.7% specificity (AUC was 0.93). Only the admission NGAL measurement in acute decompensated HF was important to foresee AKI.<sup>24</sup> Hospitalized acute decompensated HF patients might have high admission serum NGAL levels despite normal admission creatinine values.<sup>22</sup> Serum and urine NGAL levels were found to be important to foresee disease progression in chronic kidney disease patients.<sup>25</sup> Higher NGAL levels were also associated with NYHA

functional class, acute decompensation, systolic blood pressure, ejection fraction and mortality and proposed as a marker for cardiovascular risk classification.<sup>26,27</sup> Urine NGAL levels in HF patients were also positively correlated with NT-proBNP levels.<sup>28</sup> The superiority of NGAL when compared to other biomarkers is, its levels do not change with i.v. diuretic therapy.<sup>29</sup>

There is not a well-accepted cut-off value for urine NGAL. In this cohort of patients, urine NGAL had highest positive predictive value to foresee AKI at a cut-off value of 12 ng/mL. On single logistic regression analyses, urine NGAL  $\geq 12$  ng/mL cut-off value had an odds ratio of 8.9, multiple logistic regression analysis odds ratio of NGAL levels in predicting AKI was found to be 10.9. Several studies in the literature suggest cut-off values ranging between 25 and 353.5 ng/mL.<sup>30,31</sup>

In daily practice, furosemide might be withheld in patients with increasing creatinine levels, yet the mechanism might be increasing congestion of the kidneys and the increased requirement for diuretic treatment in the context of type 2 CRS. Although first day mean i.v. furosemide doses were similar between groups (80 mg), diuretic dose increment was less on the following days in AKI group. This may be due to giving less diuretics after noticing increasing creatinine values not to deteriorate renal functions more or these patients developed more AKI due to less diuretic doses due to congestion. Although we could not demonstrate an association between the NGAL level and the diuretic dose requirement, this may be demonstrated in larger patient populations.

The study has some limitations. First, the sample size was relatively small. Second, we could not confirm the diagnosis of acute decompensated HF with echocardiographic measurements. However, the strength of the study was its real-life setting, very few exclusion criteria and the prospective nature.

## Conclusion

One-fifth of patients in this real-life cohort of acute decompensated HF patients developed AKI in the first 72 h and urine NGAL was a valuable biomarker to predict the development of AKI.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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