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Novel Urinary Biomarkers in Detecting Acute Kidney Injury, Persistent Renal Impairment and All-cause Mortality following Decongestive Therapy in Acute Decompensated Heart Failure

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Abstract

Background—New urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1) and interleukin-18 (IL-18) are proposed to allow a more reliable early diagnosis and prognosis of acute kidney injury (AKI) in acute decompensated heart failure (ADHF). Our aim was to compare the predictive value of urinary NGAL, KIM-1 and IL-18 for the occurrence of AKI, persistent renal impairment and mortality in ADHF.

Methods and Results—Eighty-three patients admitted for ADHF were analyzed. Urinary creatinine (Cr), NGAL, KIM-1 and IL-18 were measured at baseline. Serum Cr was measured daily during the next 4 days and again at outpatient follow-up after 6 months. Mortality data were prospectively collected. Urinary NGAL, KIM-1 and IL-18 were modestly correlated with each other (Spearman's $\rho \leq 0.61$) and poorly correlated to estimated glomerular filtration rate (eGFR; Spearman's $\rho \leq 0.28$). None predicted AKI defined as a 25% decrease in eGFR during index hospitalization, but urinary IL-18/Cr was the strongest predictor of persistently elevated serum Cr≥0.3 mg/dL after 6 months compared to baseline (AUC=0.674; p=0.013). Urinary IL-18 was also associated with all-cause mortality (HR 1.48, 95%CI 1.16–1.87; p=0.001).

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Conclusions—Like urinary NGAL, urinary KIM-1 and IL-18 are relatively modest predictors of AKI in ADHF. Among these novel renal biomarkers examined, further investigations regarding the prognostic value of urinary IL-18 are warranted.

Keywords

Acute decompensated heart failure; acute kidney injury; biomarkers; outcome

INTRODUCTION

Changes in serum creatinine (Cr) have been the traditional method to monitor renal function during decongestive therapies in patients presenting with acute decompensated heart failure (ADHF). Worsening renal function (WRF), often defined as a 0.3 mg/dL rise in Cr, is a common finding in this context[1]. However, apart from structural damage to the nephron (i.e. "kidney injury"), it might reflect impaired renal hemodynamics (i.e. "pre-renal" azotemia), hemoconcentration, or a combination of these. Importantly, those causes of elevated Cr differ in reversibility and are difficult to discriminate by the Risk, Injury, Failure, Loss of kidney function and End-Stage kidney disease (RIFLE) criteria for acute kidney injury (AKI)[2]. This is probably one of the main reasons why the prognostic impact of WRF, defined as a Cr change, differs among subgroups of patients with ADHF[3–5].

Recently, new biomarkers have been proposed to improve the diagnosis of AKI and differentiate structural renal damage from "pre-renal" insufficiency or hemoconcentration. Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa protein secreted by renal tubular cells, leucocytes, and several other types of epithelial cells in response to ischemic or toxic injury[6]. Because NGAL is normally reabsorbed by the proximal tubules after glomerular filtration, increased urinary NGAL levels reflect impaired proximal reabsorption or increased production in distal nephron segments. On the other hand, kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein belonging to the immunoglobulin gene superfamily[6]. It is expressed on the apical membrane ciliae of proximal tubules in case of injury, but not in the normal kidney. In addition, interleukin-18 (IL-18) is a pro-inflammatory cytokine, produced by renal tubular cells and macrophages[6]. IL-18 appears to play a role in apoptosis, ischemia/reperfusion, infection, autoimmune conditions and malignancy. Both urinary NGAL and urinary KIM-1 have been demonstrated to be increased in congestive heart failure, even when estimated glomerular filtration rate (eGFR) is within the normal range, and prior reports have suggested that elevated levels are associated with poor clinical outcomes[7].

In ADHF patients, we have previously reported a rise in urinary NGAL preceding AKI during hospital admission[8]. However, this rise was only marginal compared with reports from patients with other AKI causes, suggesting only a low degree of renal tubular injury in ADHF. Others have suggested that the combination of urinary NGAL and urinary IL-18 might allow a more reliable early diagnosis and prognosis of AKI[9]. Yet no study has directly compared the urinary biomarkers NGAL, KIM-1, and IL-18 in a head-to-head manner in the setting of ADHF. Therefore, the aim of the present study was to assess and compare their predictive value for the incidence of AKI, persistent renal impairment and all-cause mortality in patients admitted with ADHF.

METHODS

Study population

Patients were eligible for enrollment within 24 h of presentation. Other inclusion criteria were: (1) age ≥18 years; (2) a planned strategy for treatment with intravenous furosemide

because of clinical evidence of congestion. Exclusion criteria were: (1) a concurrent diagnosis of an acute coronary syndrome; (2) cardiogenic shock or need for inotropes; (3) a history of cardiac transplantation and/or ventricular assist devices; (4) renal replacement therapy at any time point during or before the index hospitalization; (5) exposure to nephrotoxic agents (i.e. contrast dye); (6) urinary tract infection or bacteremia.

Study design

The Cleveland Clinic Institutional Review Board approved the study and all subjects provided written informed consent. After enrollment, demographics, clinical history, relevant co-morbid conditions, pharmacological therapy, documented left ventricular ejection fraction and a previous serum creatinine value from the last outpatient visit (≤3 months) were collected. Urine and venous blood samples were obtained at the time of admission for baseline measurements, including serum cystatin C, plasma B-type natriuretic peptide (BNP), as well as urinary NGAL, urinary KIM-1, and urinary IL-18. Absolute urinary biomarker levels were subsequently corrected for urinary creatinine and ratios expressed per gram of creatinine. Cr measurements were repeated daily during the next 4 days and again after 6 months of follow-up during an outpatient visit as part of routine clinical care. eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[10]. Treatment regimens, including timing, dosage, and route of diuretic therapy, were at the discretion of the treating physician independent of the renal or urinary biomarkers or BNP levels.

Biomarker assays

All laboratory analyses were performed with investigators blinded to cardio-renal indices and clinical outcome data. Serum cystatin C levels were determined with a particle-enhanced immunoturbidimetric immunoassay on the Architect ci8200 platform (Abbott Laboratories, Abbott Park, IL). Briefly, latex particles are coated with anti-human cystatin C antibody (Diazyme Laboratories, Poway CA) and agglutinate with cystatin C present in patients' sample. The analytical range of this assay spans 0.05 mg/L to the highest calibration point. Intra- and inter-assay coefficients are 3 % and 6 %, respectively. BNP levels were measured using the same immunoassay platform. Urinary NGAL levels were measured by an enzyme-linked immunosorbent assay (Cat. No. KIT 036, BioPorto Diagnostics, Gentofte Denmark). The minimum detection limit of the assay was 4 pg/mL. Intra-and inter-assay coefficients of variation were 1.1% and 3.2%, respectively, at 65 ng/mL. KIM-1 was measured by the Quantikine Human TIM-1 Immunoassay (R&D Systems Inc., Minneapolis, MN) with a functional sensitivity of ≤0.046 ng/mL and a total coefficient of variation <8%. The human IL-18 ELISA Kit (Medical & Biological Laboratories, Woburn MA) was used to assess urinary IL-18. This assay has a functional sensitivity of 12.5 pg/mL with a total coefficient of variation of <11%.

Study end-points

First, we assessed the correlation between urinary biomarker levels with each other, as well as with eGFR. Second, we compared the accuracy of each biomarker to predict (1) AKI, defined as a ≥25% decrease in eGFR during day 1–5; (2) persistent renal impairment, defined as persistently elevated Cr levels (≥0.3 mg/dL) after 6 months compared to baseline; and (3) all-cause mortality.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation if normally distributed or otherwise by median [interquartile range (IQR)]. Normality was assessed by the Shapiro-Wilk statistic. Categorical variables were expressed as percentages. The student's *t*-test,

Mann-Whitney *U* test, Fisher's exact test and Pearson's χ^2-test were used when appropriate to compare between groups. Correlations were assessed using Spearman's ρ. Statistical significance was set at a 2-tailed probability level of <0.05. Receiver-operated characteristic curve analysis was used to compare urinary biomarkers as predictors for AKI, and persistent renal impairment, respectively. The Cox proportional hazards model was used to calculate the hazard ratio (HR) with corresponding 95% confidence interval (95%CI) for all-cause mortality. We included all baseline characteristics and urinary biomarker levels at admission in a univariate model. All statistics were performed using IBM® SPSS® (version 20.0) for Windows.

RESULTS

Study population

We enrolled 90 patients who fulfilled inclusion and exclusion criteria. Seven patients were subsequently excluded because of missing data. In one patient, measurement of urinary biomarkers was not done as the urinary sample was discarded accidently. In another patient, only one serum creatinine measurement (baseline) was available and therefore the end-point of AKI could not be determined. Finally, KIM-1 measurements were lacking in 5 other patients. Those 7 patients had similar baseline characteristics compared to the study population analyzed. All of them were alive at the end of follow-up. Inclusion of these patients in the analyses rendered similar results. Therefore, the final analysis encompasses 83 patients with complete data. Baseline characteristics and pharmacological therapy of the study population are summarized in Table 1. Baseline Cr was 1.32 mg/dL (1.03–2.19 mg/dL), corresponding to an eGFR of 57±29 mL/min/1.73m^2. Serum cystatin C was 2.14±0.80 mg/dL, which corresponded to the same eGFR. In contrast, median (IQR) Cr was 1.14 mg/dL (0.99–1.48 mg/dL) at the moment of the last outpatient evaluation preceding the index hospitalization, corresponding to an eGFR of 65±26 mL/min/1.73m^2.

Correlation between urinary biomarkers and eGFR

We observed only moderate correlations between different urinary biomarkers and each other (Table 2). Overall, biomarker levels were relatively low at the time of admission: urinary NGAL was 12.3 ng/mL (5.6–27.4 ng/mL) or 2.0 ng/g$_{Cr}$ (0.6–7.5 ng/g$_{Cr}$); urinary KIM-1 was 0.68 ng/mL (0.17–1.78 ng/mL) or 0.30 ng/g$_{Cr}$ (0.07–1.02 ng/g$_{Cr}$); and urinary IL-18 was 26.37 pg/mL (10.97–46.56 pg/mL) or 7.05 pg/g$_{Cr}$ (2.90–11.82 pg/g$_{Cr}$). Both absolute urinary biomarker levels and values corrected for Cr were poorly correlated to eGFR (Table 3).

Prediction of AKI with urinary biomarkers

Fourteen patients (17%) experienced AKI during the first 5 days of the index hospitalization. Patients who developed AKI had a lower baseline blood urea nitrogen compared to patients who did not (28±14 mg/dL versus 45±14 mg/dL, respectively; p=0.007), but other baseline characteristics were similar. Figure 1 shows the evolution of the eGFR over time according to the development of AKI. Patients with AKI tended to have an improvement in renal function at follow-up (ΔeGFR=+6±25 mL/min/1.73m^2; p=0.386). In contrast, patients without AKI experienced a non-significant decrease in eGFR at follow-up (ΔeGFR=-2±23 mL/min/1.73m^2; p=0.421). Comparing all urinary biomarkers with or without creatinine adjustment, none had adequate sensitivity/specificity to predict AKI (Figure 2). The length of hospital stay was 11 days (8–15 days) in patients with versus 9 days (5–19 days) in patients without AKI (p=0.860 for the difference).

Prediction of persistent renal impairment with urinary biomarkers

After 6 months, 25 patients (31%) had a persistently elevated Cr level (≥0.3 mg/dL) compared to baseline. Those patients had significantly higher baseline BNP levels [1,150 pg/mL (792–2145 pg/mL)] compared to patients without persistent renal impairment [809 pg/mL (370–1408 pg/mL); p=0.043 for the difference between groups]. Other baseline characteristics were similar among both groups. Figure 3 shows the evolution of the eGFR over time according to the presence of persistent renal impairment. Patients with persistent renal impairment had a gradual and significant decline in eGFR during the index hospitalization (ΔeGFR=−6±12 mL/min/1.73m^2; p=0.028). In contrast, patients without persistent renal impairment had no significant change in eGFR (ΔeGFR=+2±16 mL/min/1.73m^2; p=0.478). Urinary IL-18, especially when corrected for creatinine, was the only urinary biomarker with acceptable sensitivity/specificity to predict persistent renal impairment (Figure 4). At an optimal cut-off value of 7 pg/g$_{Cr}$ (comparable to the median value in the population), urinary IL-18 had 68% sensitivity and 60% specificity to predict persistent renal impairment.

All-cause mortality

During 7±4 months of follow-up, 31 patients died (37%). The results of univariate analysis for baseline characteristics to predict all-cause mortality are presented in Table 4. Only urinary IL-18 (HR 1.48, 95%CI 1.16–1.87; p=0.001) was significantly associated with all-cause mortality. In addition, persistent renal impairment (HR 2.23, 95%CI 1.07–4.66; p=0.032) but not AKI (HR 1.37, 95%CI 0.56–3.36; p=0.488) was significantly correlated to all-cause mortality.

DISCUSSION

The key finding of this prospective cohort study of patients admitted with ADHF is that novel urinary biomarkers that reflect renal tubular injury are generally poor predictors of in-hospital AKI as defined by Cr levels. Only urinary IL-18/Cr had a modest predictive value for persistent renal impairment after 6 months of follow-up, which was more consistently associated with all-cause mortality than AKI. In contrast, urinary NGAL and urinary KIM-1 did not reliably predict persistent renal impairment or all-cause mortality.

Our group and others have identified the association between elevated serum NGAL levels and the occurrence of WRF in patients with ADHF [11]. Even though earlier work has implied that serum and urinary NGAL levels as well as eGFR are correlated in patients with ischemic heart failure [12], new evidence has suggested that serum and urinary NGAL represent different aspects of the nephron's function. While higher serum NGAL correlates well to reduced glomerular filtration function, urinary NGAL is more like a marker of impaired natriuresis and diuresis in the setting of ADHF [13]. Although it has been well described that urinary NGAL levels are higher in heart failure patients than in healthy volunteers, correlations with other markers of renal tubular damage (i.e. urinary albumin excretion) are very poor and the rise of urinary NGAL during decongestive treatment is very modest, even in case of WRF, when compared with other AKI causes [8, 14, 15]. Indeed, in most patients admitted for ADHF, urinary NGAL levels remain well below the cut-off proposed to predict AKI after cardiac surgery, which is 50–213 ng/mL [8, 16, 17]. There is similar but less evidence regarding KIM-1 as a marker for tubular injury in ADHF. Urinary KIM-1 levels are higher in heart failure patients compared with controls, even when eGFR is within the normal range, but still levels remain well below the proposed cut-off of 7 ng/g Cr for predicting AKI [7, 14, 18, 19]. Our findings confirm that urinary NGAL, urinary KIM-1, and urinary IL-18 are generally lower in patients who present with ADHF than those reported in the literature with AKI, which suggests that AKI in ADHF is likely due to other causes than

structural tubular damage. Indeed, hemodynamics that determine renal blood flow (both renal perfusion and venous congestion) show a better correlation with renal function and make a stronger plead for a phenotype of "pre-renal" azotemia [20, 21].

Clinical importance of the current study

Our study adds several new findings to the current literature for these novel renal biomarkers. First, for the first time the patterns of urinary NGAL, urinary KIM-1, and urinary IL-18 are compared in a head-to-head manner in the setting of ADHF and their predictive value for AKI and short-term mortality is assessed. We demonstrated that those urinary biomarkers correlate only moderately with each other, suggesting that they reflect different functional aspects of the nephron or the fact that they have a wide range of analytical variability. All the biomarkers demonstrated relatively poor correlations with eGFR, which could be expected from specific biomarkers of renal tubular damage. Second, we analyzed an end-point of persistent renal impairment. It has been clearly demonstrated from a sub-analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) that post-discharge WRF or AKI has a much stronger prognostic value than WRF or AKI during hospitalization [22]. Indeed we showed that eGFR tended to improve in patients with AKI defined as a ≥25% decrease in eGFR during day 1–5 of the index hospitalization, although this remained associated with a (non-significant) 37% increase in all-cause mortality. In contrast, persistent renal impairment, defined as a persistently elevated Cr (≥0.3 mg/dL) after 6 months compared to baseline increased all-cause mortality more than twofold, a finding that was statistically significant. This is reassuring for those that experience WRF during hospitalization whereby achieving recovery of renal function may occur beyond hospitalization. Third, our data suggest that urinary IL-18 might be a better predictor for persistent renal impairment and all-cause mortality when compared to urinary NGAL or urinary KIM-1. Urinary IL-18/Cr at a cut-off similar to the median (7 ng/g_{Cr}) had a modest 68% sensitivity and 60% specificity to predict persistent renal impairment after 6 months.

Parikh et al. were the first to suggest that urinary IL-18 might be a useful early diagnostic marker for AKI in the intensive care unit [23]. Previously, it had been showed in animal models that IL-18 mediates ischemic acute tubular necrosis and that impaired IL-18 processing protects caspase-1-deficient mice against deterioration of renal impairment [24, 25]. This active involvement in the pathophysiology of ischemic acute tubular necroses, the type of tubular injury one would most expect from impaired hemodynamics in ADHF, might explain why urinary IL-18 performed better than urinary NGAL and urinary KIM-1 in our population. Moreover, the well-known correlation between serum IL-18 and myocardial dysfunction, atherogenesis, plaque rupture, and ischemia-reperfusion injury might further strengthen its value as a prognostic marker in ADHF [26–29]. In contrast, both urinary NGAL and urinary KIM-1 were not significantly associated with all-cause mortality. Therefore, further studies in the role of urinary IL-18 in ADHF are warranted.

Study limitations

Our results should be interpreted in the light of some study limitations. First, our renal end-points were based on serum creatinine measurements, which are influenced by age, gender, ethnicity, muscle mass, diet and tubular secretion apart from glomerular filtration [30]. However, we calculated eGFR, using the most accurate formula currently available (CDK-EPI) [10]. Further, baseline serum creatinine and calculated eGFR were validated against serum cystatin C levels, which yielded an equal eGFR. Second, we obtained urinary biomarkers only at the moment of admission. Therefore, we cannot report changes over time, which might enhance the performance of those biomarkers to predict AKI or persistent renal impairment. Third, there was no clinical or histological information available about

underlying intrinsic renal disease as “gold standard” for AKI. Fourth, follow-up was only limited in time, but ≥6 months for every patient, precluding conclusions about the value of the urinary biomarkers for long-term prognosis. Also, in the absence of standardization of treatment protocol but instead according to the preferences of the treating physician, differences in the use, type and dosages of diuretics before or after baseline measurements may have influenced the results. Fifth, it should be noted that our population was predominantly male with a fair proportion of heart failure with preserved ejection fraction and relatively preserved baseline renal function. Finally, our study had a limited sample size and therefore our findings should be considered hypothesis-generating which asks for confirmation.

CONCLUSIONS

Like urinary NGAL, urinary KIM-1 and urinary IL-18 are relatively modest predictors of AKI in ADHF. Among these novel renal biomarkers examined, further investigations regarding the prognostic value of urinary IL-18 are warranted.

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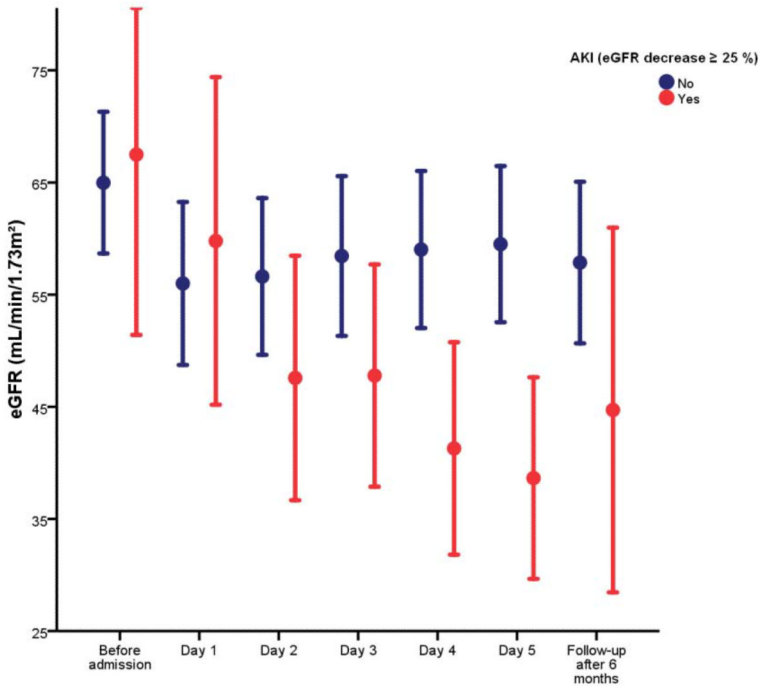
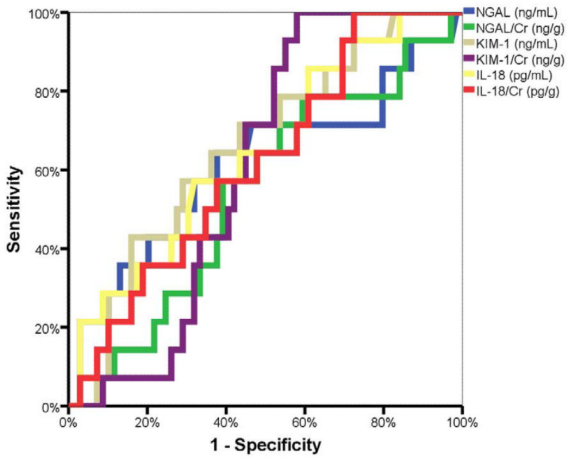


Figure 1.
Evolution of estimated glomerular filtration rate (eGFR) during hospitalization for acute decompensated heart failure (ADHF) and at follow-up according to the development of acute kidney injury (AKI) defined as ≥25% decrease in eGFR.



NGAL	AUC = 0.615 (0.434-0.796)	p=0.177
NGAL /Cr	AUC = 0.541 (0.382-0.700)	p=0.627
KIM-1	AUC = 0.658 (0.511-0.805)	p=0.064
KIM-1/Cr	AUC = 0.607 (0.488-0.725)	p=0.210
IL-18	AUC = 0.643 (0.489-0.798)	p=0.092
IL-18/Cr	AUC = 0.618 (0.471-0.765)	p=0.166

Figure 2.
Receiver-operated characteristic (ROC) curve analysis for urinary biomarkers to predict AKI.

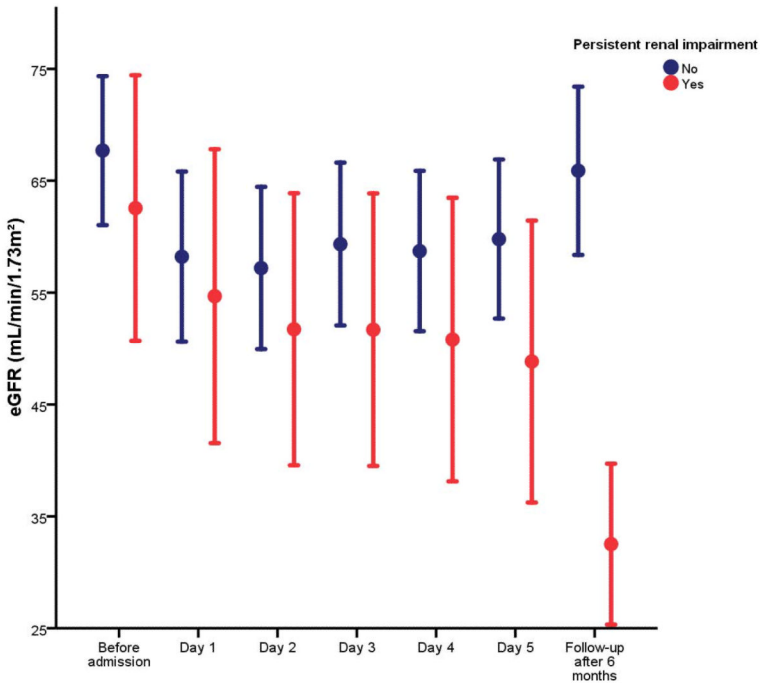
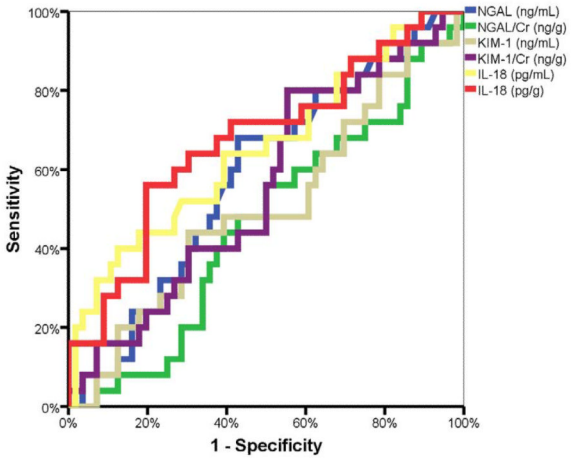


Figure 3.

Evolution of eGFR during hospitalization for ADHF and at follow-up in patients with versus without persistent renal impairment defined as ≥0.3 mg/dL increase in serum creatinine after 6 months compared to baseline.



NGAL	AUC = 0.584 (0.453-0.715)	p=0.228
NGAL /Cr	AUC = 0.461 (0.327-0.594)	p=0.574
KIM-1	AUC = 0.504 (0.365-0.643)	p=0.951
KIM-1/Cr	AUC = 0.556 (0.423-0.690)	p=0.419
IL-18	AUC = 0.652 (0.519-0.786)	p=0.029
IL-18/Cr	AUC = 0.674 (0.543-0.805)	p=0.013

Figure 4.
ROC curve analysis for urinary biomarkers to predict persistent renal impairment.

Table 1

Baseline characteristics and pharmacological therapy of the study population (n=83)

Baseline characteristics		
Age (years)		64±15
Gender		
	Male	73%
	Female	27%
Ethnicity		
	White	68%
	Black	31%
	Asian	1%
Body mass index (kg/m^2)		30±9
Hypertension		68%
Diabetes mellitus		43%
Ischemic etiology of heart failure		40%
Left ventricular ejection fraction (%)		31±17
Left ventricular ejection fraction >40%		28%
Plasma brain natriuretic peptide (pg/mL)		881 (450–1,899)
Atrial fibrillation		37%
Chronic obstructive pulmonary disease		15%
Blood urea nitrogen (mg/dL)		43±25
Renal function – KDOQI class *		
	I (eGFR ≥90 mL/min/1.73m^2)	19%
	II (eGFR 60–89 mL/min/1.73m^2)	41%
	IIIa (eGFR 45–59 mL/min/1.73m^2)	12%
	IIIb (eGFR 30–44 mL/min/1.73m^2)	19%
	IV (eGFR 15–29 mL/min/1.73m^2)	7%
	V (eGFR <15mL/min/1.73m^2)	1%
Pharmacological therapy		
Angiotensin-converting enzyme inhibitor		34%
Angiotensin II receptor blocker		12%
β-blocker		65%
Mineralocorticoid receptor antagonist		29%
Digoxin		24%
Loop diuretic		81%
Vasodilator		29%
Aspirin		58%
Statin		43%
Calcium channel blocker		13%

* KDOQI, Kidney Disease Outcomes Quality Initiative; eGFR, estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula based on the last serum creatinine value available preceding the index admission

Table 2

Spearman's correlation between urinary biomarkers head to head

	NGAL/Cr	KIM-1	KIM-1/Cr	IL-18	IL-18/Cr
NGAL	ρ=0.75	ρ=0.42	ρ=−0.23	ρ=0.30	ρ=0.05
	p<0.001	p<0.001	p=0.035	p=0.006	p=0.637
NGAL/Cr		ρ=0.23	ρ=−0.57	ρ=−0.24	ρ=−0.56
		p=0.035	p<0.001	p=0.033	p<0.001
KIM-1			ρ=0.61	ρ=0.49	ρ=0.18
			p<0.001	p<0.001	p=0.108
KIM-1/Cr				ρ=0.61	ρ=0.57
				p<0.001	p<0.001
IL-18					ρ=0.79
					p<0.001

Cr, serum creatinine; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin

Table 3

Spearman's correlation between urinary biomarkers and estimates of glomerular filtration rate

	Serum Cr	$eGFR_{Cr}$	Serum Cystatin C	$eGFR_{CysC}$
NGAL	ρ=0.17	ρ=−0.22	ρ=0.28	ρ=−0.28
	p=0.122	p=0.048	p=0.012	p=0.012
NGAL/Cr	ρ=0.27	ρ=−0.28	ρ=0.26	ρ=−0.26
	p=0.015	p=0.009	p=0.023	p=0.022
KIM-1	ρ=−0.03	ρ=−0.01	ρ=0.07	ρ=−0.08
	p=0.790	p=0.925	p=0.523	p=0.467
KIM-1/Cr	ρ=−0.21	ρ=0.19	ρ=−0.15	ρ=0.14
	p=0.055	p=0.078	p=0.190	p=0.207
IL-18	ρ=−0.26	ρ=0.23	ρ=−0.15	ρ=0.15
	p=0.020	p=0.040	p=0.198	p=0.192
IL-18/Cr	ρ=−0.19	ρ=0.14	ρ=−0.01	ρ=0.01
	p=0.080	p=0.224	p=0.925	p=0.909

Cr, serum creatinine; IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin

Table 4

Significant predictors of all-cause mortality in univariate analysis

	Univariate HR* (95 % CI)	P-value
Male gender	0.56 (0.27–1.19)	0.131
Ejection fraction (%)	1.26 (0.90–1.77)	0.186
Baseline plasma BNP (pg/mL)	1.28 (0.93–1.75)	0.132
Baseline serum Cystatin C (mg/L)	1.37 (0.97–1.93)	0.072
Baseline urinary NGAL (ng/mL)	1.26 (0.97–1.64)	0.079
Baseline urinary KIM-1 (ng/mL)	1.29 (0.98–1.71)	0.072
Baseline urinary IL-18 (pg/mL)	1.48 (1.16–1.87)	0.001

BNP, brain natriuretic peptide; uNGAL, urinary neutrophil gelatinase-associated lipocalin; uKIM-1, urinary kidney injury molecule-1; uIL-18, urinary interleukin-18

*HR for continuous variables expressed per standard deviation change