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Activation Pattern of Candidate Renal Biomarkers in Acute Heart Failure: Superiority of Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Carsten G Jungbauer*, Michael Brand, Maximilian Schwiede, Stefan Stadler, Monika Buesing, Günter Riegger, Lars S. Maier and Andreas Luchner

Clinic for Internal Medicine II - Cardiology, University Hospital Regensburg, Germany

***Corresponding author:** Dr. Carsten Jungbauer, M.D., Clinic for Internal Medicine II - Cardiology, University Hospital Regensburg , Germany, Tel: ++49 941 944-7211; Fax: ++49 941 944-7213; Email: carsten.jungbauer@klinik.uni-regensburg.de

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Abstract

Background: Patients with acutely decompensated heart failure often suffer from deterioration in renal function, also referred to as cardiorenal syndrome (CRS). The aim was to assess and compare a set of investigational markers of acute kidney injury (AKI) in acute heart failure (AHF).

Methods: The renal biomarkers Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney injury molecule-1 (KIM-1), N-acteyl-ß-D-glucosaminidase (NAG) and Interleukin-18 (Il-18) were assessed from urine samples of 58 patients with AHF and 54 healthy controls.

Results: Upon admission, NGAL, KIM-1 and NAG, but not Il-18 (p= n.s.), were significantly elevated in patients with AHF as compared to healthy controls (each p<0.05). The candidate renal markers were neither significantly correlated with established renal parameters (creatinine, cystatin C and eGFR) nor with proteinuria markers (urinary protein, albumin). Among all 58 patients, 23 (40%) patients developed acute kidney injury, as defined by increase of serum creatinine > 0.3 mg/dL. Only NGAL at day 2 and during the middle of therapy was significantly elevated in AKI patients (each p<0.05), whereas KIM-1, NAG and Il-18 did not differ (all p= n.s.). Upon logistic regression analysis, NGAL at day 2 predicted developing AKI significantly and independently from age and eGFR (each p<0.01). Upon ROC analysis, NGAL at the day before creatinine rise predicted AKI with a sensitivity of 83% and specificity of 78% (AUC 0.75). There was no association between NGAL and cumulative diuretic dosis, length of i.v. diuretic therapy or hospital stay.

Conclusions: NGAL, KIM-1 and NAG, but not Il-18 are elevated in patients with acute heart failure. This finding is independent from eGFR and serum creatinine and indicates tubular injury in acute heart failure. Among these candidate renal biomarkers, NGAL performs exceptionally well over the other investigational renal biomarkers to detect acute kidney injury.

Keywords: NGAL; Renal biomarkers; Heart failure; Kidney injury

Abbreviations

ACE-I: ACE-Inhibitor**;** ADHF: Acute Decompensate Heart Failure; AKI: Acute Kidney Injury; ARTB: Angiotensin Receptor Blocker; EF: Ejection Fraction; CRS: Cardio Renal Syndrome; eGFR: estimated Glomerular Filtration Rate; Il-18: Interleucin 18; JVP: Jugular Venous Pressure; KIM-1: Kidney Injury Molecule-1; LVD: Left Ventricular Dysfunction; NAG: N-acteyl-ß-D-glucosaminidase; NGAL: Neutrophil Gelatinase-Associated Lipocalin; NT-pro BNP: N-Terminal Brain Natriuretic Peptide; RAAS: Renin-Angiotensin-Aldosterone-System; UCr: Urinary Creatinine

Introduction

Acute heart failure is often characterized by concomitant renal dysfunction and many patients admitted with acutely decompensated heart failure (ADHF) are prone to develop acute kidney injury (AKI) [1, 2, 3]. Also, chronic kidney disease predisposes to AKI in 30-40% of cases [4]. AKI is associated with short and long term morbidity and mortality and increase of healthcare costs [5, 6]. The early diagnosis of developing AKI in ADHF is difficult to achieve because the established renal biomarker, serum creatinine (sCr), has only suboptimal ability to detect AKI in time and to quantify its severity accurately. Candidate renal biomarkers are currently under investigation in the setting of ADHF to improve early detection of AKI and cardiorenal syndromes.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is an almost 25 kDa low-molecular-weight-Protein, which is part of the lipocalin superfamily and rises 24 to 48 hours before creatinine in patients with AKI [8, 9, 10, 11]. Kidney injury molecule-1 (KIM-1), a transmembrane glycoprotein, will appear in urine after acute or chronic renal injury [12,13,14]. KIM-1 seems to be specific especially for ischemic kidney injury [14]. N-acteyl-ß-D-glucosaminidase (NAG) is a large lysosomal enzyme (> 130 kDa) of the renal tubular epithelial brush border, which rises following various modalities of kidney injury [15, 16, 17]. The cytokine Interleukin-18 (Il-18) is also a biomarker for diagnosis and prognosis of AKI [18, 19, 20]. NGAL,

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Table 1: Clinical characteristics.

	Heart Failure, n = 58	Healthy controls, n=54	p-value vs whole cohort
Male	47 (81.4%)	26 (41.1%)	<0.001
Age, years	73.0 ± 11.1	50.5 ± 6.0	<0.001
Body mass index, kg/m^2	29.0 ± 7.9	24.9 ± 3.4	<0.001
Ischemic CMP	35 (59.3%)	-	
Initial eGFR	50.8 ± 25.2	108,9 ± 29,6	<0.001
eGFR before hospitalization	61.9 ± 26.5	-	
Creatinine initial, mg/dL	1.22 ± 0.58	0.86 ± 0.23	<0.001
Creatinine before hospitalization, mg/dL	1,10 ± 0.60	-	
Cystatin C, mg/L	1.48 ± 0.53	0.64 ± 0.11	<0.001
no albuminuria / mikroalbuminuria / markoalbuminuria	18 (30.5%) / 31 (52.5%) / 10 (16.9%)	54 (100%) / 0 / 0	<0.001
CKD-Stage I / II / III / IV / V	7 (12.1%) / 19 (32.8%) / 25 (43.1%) / 7 (12.1%) / 0	44 (% / 10 (%) / 0 / 0/ 0	<0.001
Time to recompensation or discharge, days	7.0 ± 2.7	-	
Fully recompensated n (%)	43 (72.9%)	-	
Cumulative weight loss, kg	5.0 ± 3.2	-	
Cumulative i.v. loop diuretic dose, mg	598 ± 778	-	
Hypertension	43 (72.9%)	0	<0.001
COPD	6 (11.9%)	0	<0.001
Pulmonary embolism	3 (5.1%)	0	<0.001
Thrombosis	9 (17.0%)	0	<0.001
Smoking	16 (28.8%)	0	<0.001
Diabetes	30 (49.2%)	0	<0.001
Stroke	6 (10.6%)	0	<0.001
Atrial fibrillation	24 (39.4%)	0	<0.001
Drug therapy			
ACE-I / ARB	45 (73.5%)	0	<0.001
Beta-blocker	50 (84.8%)	0	<0.001
Loop diuretic	54 (91.5%)	0	<0.001
Thiazide diuretic	11 (18.6%)	0	<0.001
Aldosterone antagonist	26 (44.1%)	0	<0.001
Digitalis	12 (20.3%)	0	<0.001
Calcium channel blocker	8 (13.6%)	0	<0.001
NYHA III, IV	53 (89.8%)	0	<0.001
Ejection fraction	38.8 ± 11.8%	62.2 ± 3.2	<0.001
RRsys mmHg	130 ± 19	114 ± 11	<0.001
RRdia mmHg	80 ± 19	70 ± 8	<0.001
NT-proBNP, pg/mL	3750 ± 9690	30.4 ± 37.7	<0.001
Protein, g/g Crea	242 ±1030	58.1 ± 26.2	<0.001
Albumin, mg/g Crea	68.6 ± 905.7	12.0 ± 14.6	<0.001
IgG, g/g Crea	14.0 ± 707.9	4.1 ± 4.6	<0.001
A1-Microglobulin, g/g Crea	16.7 ± 36.6	8.2 ± 6.9	<0.001
KIM-1, ng/g Crea	1170 ± 2270	401 ± 611	<0.001
NAG, U/g Crea	5.4 ± 12.1	1.3 ± 4.4	<0.001
NGAL, µg/g Crea	18.1 ± 68.4	10.8 ± 16.6	=0.006
Il-18, ng/g Crea	29.4 ± 63.0	27.8 ± 34.4	n.s.

KIM-1, NAG and Il-18 are earlier and more sensitive indicators of renal injury than plasma creatinine and predominantly indicate tubular injury [21]. Initially, these new urinary biomarkers were identified and evaluated in patients with acute kidney injury and hereby especially in cardiac surgery patients [8, 18, 19].

The aim of the present study was to assess the potential of these four candidate renal biomarkers to detect evolving AKI in patients with ADHF. All markers were assessed with sequential measurement in a cohort of well phenotyped patients with ADHF and close clinical assessment throughout the hospitalization.

Methods

Patient population

Patients diagnosed with acute congestive heart failure were enrolled in this prospective, observational, un-blinded study within 6 hours of arrival at university hospital Regensburg. All of the participating patients were older than 18 years of age with a necessity of treatment including intravenous loop diuretics due to acute heart failure. The patients had to show congestive symptoms that included elevated jugular venous pressure, peripheral edema, pulmonary rales and/or ascites. Patients with acute coronary syndromes, necessity of exposure to contrast media and end-stage renal disease with regular dialysis therapy were excluded. The study was approved by the institutional ethics committee and performed in agreement with good clinical practice guidelines and with the standards established for human experimentation by the Declaration of Helsinki.

Study design

All enrolled patients provided written consent. 64 patients and 54 healthy controls were initially enrolled. 6 patients were excluded due to incomplete data collection or contrast media exposure leaving 58 eligible patients that participated in the final analysis. Treatment of all patients was in accordance with the local therapy standard and at the discretion of the treating physician, e.g. dosis of loop diuretics, timing and continuous or intermittent administration. Serum and urine samples were obtained immediately after enrollment for day 1 measurements. Subsequent samples were collected on day 2, in the middle and at the end of the recompensation therapy. Serum and morning urine spot samples were collected simultaneously in each case.

Weight loss of each patient was documented on a daily basis. Further, each patient was followed-up daily and clinical data that included vital signs, presence of edema, rales, elevated jugular venous pressure and NYHA stage as well as significant investigations or interventions, especially contrast medium exposure, were noted.

The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renals disease equation (MDRD).

AKI was defined, using the Acute Kidney Injury Network criteria, as an absolute increase in plasma creatinine above baseline of at least 0.3 mg/dl or a percentage increase of at least 50% [23, 24]. A relevant serum creatinine rise was identified if it occurred within the first 72 hours of hospitalization. The admission serum creatinine at baseline or to a previous serum creatinine value obtained from outpatient visits during the previous three months was used to ascertain any rises.

Sample processing and biochemical analyze

Blood and urine samples from spontaneous morning voids were collected simultaneously at every sampling point (day 1, day 2, middle and end of therapy). Blood and urine samples were sent to the central laboratory directly after collection. The central laboratory performed a same day analysis of serum and urinary creatinine, cystatine C, NT-proBNP and urinary proteins (total protein, albumin, alpha1-microglobulin and IgG).

Urine samples were also collected from spontaneous voids and centrifuged. Urine supernatant was aliquoted into 2 ml tubes and frozen at -80 °C. At the time of assay, the samples were thawed, vortexed and centrifuged at 14000 g at 4 °C. Samples for KIM-1 (kidney injury molecule-1) were diluted 1:3 and determined with KIM ELISA KIT (R&D Systems, UK). The NAG (ß-N-Acetylglucosamidase) assay was determined with NAG colorimetric assay KIT (Roche, Mannheim). Samples for NGAL (Neutrophil Gelatinase-Associated Lipocalin) were diluted 1:100 and determined with NGAL ELISA KIT (Bio Porto, Denmark). Il-18 (interleucin 18) was analysed with IL-18 ELISA Kit (MBL, Japan). All of the aforementioned assays were performed in accordance with the manufacturer's instructions respectfully. Also, all biomarkers were normalized to urinary creatinine in order to minimize dilutional bias.

Statistics

Descriptive data are presented as mean (+/-SD), medians (+/-SD) or percentages. Correlation coefficients were calculated according to Spearman. Normally distributed values were evaluated with the Student´s unpaired two-sided T-test. The Mann-Whitney-U-test was used in the case of continuous not-normally distributed variables. For comparison of related samples the Wilcoxon signed-rank test was used in the case of non-parametric variables. To analyze and visualize the differences between different measurements at day 1, day 2, in the middle and the end of the study, box-plot analyses were performed.

Data was analyzed using commercially available statistical software packages (SPSS 17.0, SPSS Inc., Chicago, Illinois and MedCalc 8.0, MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics (Tables 1 and 2)

58 patients and 54 healthy controls were included into the analysis. Table 1 summarizes the baseline characteristics. Median age was 73 years (IQR 62-77 years) and 47 patients (81.4%) were male.

23 patients (39.7%) suffered from AKI, but none of the patient's required dialysis. 10 patients showed AKI immediately upon hospital admission and further 13 patients developed AKI during the first 72 hours of their hospital stay. Patients with subsequent AKI showed significantly decreased renal function at baseline in comparison to patients without AKI. There were no further significant differences regarding baseline parameters between both groups.

Patients were treated for a median of 6 days with cumulative 598 mg (IQR 360-830 mg) intravenous furosemide. The median weight loss was 5.0 kg (IQR 3.1-7.3 kg). Biomarker concentrations were significantly higher in patients than in healthy controls (each $p<0.05$), except for Il-18 (p= n.s.). No relevant biomarker concentration

Table 2: Patient characteristics according to development of AKI.

	No AKI, n=35	AKI, n=23	P- value AKI vs no AKI
Male	29 (82.9%)	18 (78.3%)	n.s.
Age, years	74.0 ± 12.1	72.0 ± 9,8	n.s.
Body mass index, kg/m^2	29.8 ± 7.1	27.8 ± 7.1	n.s.
Ischemic CMP	21 (60%)	14 (60.9%)	n.s.
Initial eGFR	69.9 ± 27.2	37.7 ± 16.1	<0,001
eGFR before hospitalization	66.0 ± 24.7	47.9 ± 22.4	=0.022
Creatinine initial, mg/dL	1.00 ± 0.48	1.60 ± 0.57	<0,001
Creatinine before hospitalization, mg/dL	1.06 ± 0.54	1.59 ± 0.64	=0.019
Cystatin C, mg/L	1.17 ± 0.42	1.76 ± 0.55	0,002
no albuminuria / mikroalbuminuria / markoalbuminuria	8 (22.9%) / 22 (62.9%) / 5 (14.3%)	10 (43.5%) / 8 (34.8%) / 5 (21.7%)	<0,001
CKD-Stage I / II / III / IV / V	7 (20%) / 15 (42.9%) / 12 (34.3%) / 1 (2.9%) / 0	0 / 4 (17.4%) / 13 (56.5%) / 6 (26.1%) / 0	<0,001
Time to recompensation or discharge	6.0 ± 2.6	7.0 ± 2.6	n.s.
Fully recompensated n (%)	28 (80%)	15 (65.2%)	n.s
Cumulative weight loss, kg	5.0 ± 3.1	4.5 ± 3.4	n.s.
Cumulative i.v. loop diuretic dose, mg	568 ± 535	670 ± 1053	n.s.
NYHA III, IV	31 (88.6%)	21 (91.3%)	n.s.
Ejection fraction	42.0% ± 11.9%	38.0 ± 11.7	n.s.
NT-proBNP [pg/mL]	2670 ± 8310	4679 ± 11420	n.s.
protein g/g Crea	247 ± 976	219.5 ± 1117.6	n.s.
albumin mg/g Crea	64.0 ± 921.1	70.0 ± 896.4	n.s.
IgG g/g Crea	14.0 ± 908.9	15.2 ± 147.6	n.s.
A1-Microglobulin g/g Crea	16.5 ±40.4	16.8 ± 30.4	n.s.
KIM-1 ng/g Crea	1394 ± 1146	740 ± 1479	n.s.
NAG U/g Crea	6.7 ±9.1	3.6 ± 16.2	n.s.
NGAL µg/g Crea	16.8 ± 33.8	27.9 ± 93.2	n.s.
Il-18 ng/g Crea	31.2 ± 91.1	17.8 ± 325.3	n.s.

differences were evident between male and female patients and controls (each p= n.s.).

Correlation of renal biomarkers with renal and cardiac function

Neither urinary protein, albumin or IgG nor NGAL, KIM-1 and NAG were correlated with any of the renal function parameters (sCr, eGFR and Cystatin C; each correlation with p= n.s.). Only Il-18 showed a negative correlation with sCr (r=-0.29, p= 0.037) and a1-microglobulin a positive correlation with Cystatin C (r=0.29, p=0.037).

NAG was the only urinary biomarker correlated with EF (r= -0.31, p= 0.021). NAG was also correlated with NT-proBNP (r=0.31, p=0.024). Urinary protein (r=0.38, p=0.004), albumin (r= 0.39, p=0.004) and IgG (r=0.027, p=0.046) were also positively correlated with NT-proBNP. No further significant correlation could be found between other renal or cardiac parameters.

Candidate renal biomarkers in ADHF

NGAL concentrations were significantly elevated at day 2 and at middle of therapy in the AKI vs. non-AKI group (each $p < 0.05$, Figure 1). Regarding the 13 patients with in-hospital AKI (Figure 2), NGAL showed a significant increase in concentration at the day before the creatinine rise (vs. patients without AKI $p<0.05$, vs. day of creatinine rise $p< 0.05$). At all times of measurement, there were no significant differences to patients with AKI prior to hospitalization. A ROC-analysis yielded satisfying predictive values of NGAL before creatinine rise for AKI detection (Table 3).

In contrast, neither KIM-1, NAG nor IL-18 differed significantly between patients with and without AKI and no significant or relevant differences were evident between the four different times of measurement (Figure 3; p= n.s. between each sampling point, also after stratification for AKI; except for NAG between middle and end of therapy ($p <0.05$).

In a binary logistic regression analysis, NGAL at day 2 was a significant predictor for developing AKI, beside age and eGFR (each $p <0.05$, Table 4).

Further, no significant association was evident between any of the candidate renal markers and length of intravenous loop diuretic

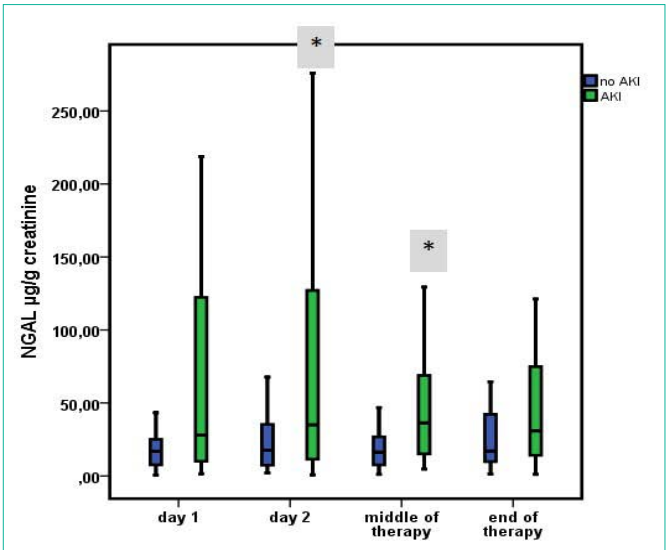

Figure 1: NGAL concentrations at different time points: no AKI vs. AKI (* vs. no AKI p <0.05).

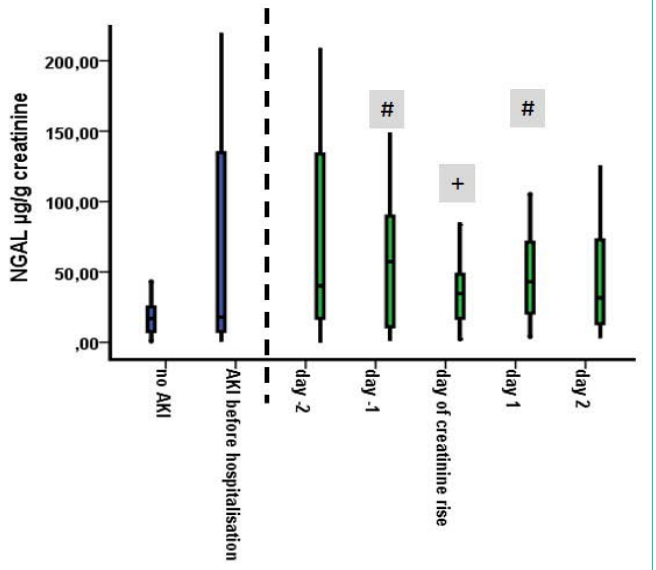

Figure 2: NGAL: patients with inhospital AKI (green) vs. patients without AKI and patients with preadmission AKI (each blue; + vs. d-1 p < 0.05; # vs. no AKI p < 0.05).

therapy, cumulative loop diuretic dosis or length of hospital stay (each p=n.s.). Also, AKI development was not associated with one of the aforementioned parameters (each p= n.s.).

Renal function parameters and proteinuria in ADHF

In patients suffering from AKI, cystatin C and sCr were significantly elevated and eGFR was significantly decreased in comparison to non-AKI-patients regarding all sampling points (each p <0.05).

Of note, in patients without AKI a decrease in protein, albumin and IgG concentrations was observed during recompensation therapy compared between the different sampling points and day 1 (each p< 0.05). This decrease was most pronounced for albumin with a gradual decrease over time. In contrast, there was no significant decrease in proteinuria evident in patients with AKI (each p= n.s.).

Table 3: ROC analysis regarding detection of inhospital AKI (NGAL at day-2 and day-1 before creatinine rise).

	AUC	Cut-off	Sens.	Spec.
NGAL d-2	0,70	27,1	75%	78%
NGAL d-1	0,75	26,5	83%	78%

NT-proBNP in ADHF

During the course of therapy, NT-proBNP decreased significantly (day 1 3746 ± 9690 pg/ml, day 2 3153 ± 9445, middle of therapy 2778 ± 9000 pg/ml, end of therapy 2589 ± 8756, each p < 0.05, except for comparison middle vs end of therapy).

Discussion

In the current study a panel of four candidate urinary biomarkers was evaluated in patients with acutely decompensated heart failure with established renal function parameters, traditional proteinuria markers and NT-proBNP. Biomarker assessment showed elevated urinary markers in ADHF compared to healthy controls. The renal biomarkers were not associated with loop diuretic cumulative dosis and length of intravenous therapy or hospital stay. In patients with ADHF and in-hospital AKI, NGAL increased one day before sCr and outperformed as marker of AKI in comparison to the other markers.

Acute kidney injury

In the current study more than one third of patients with ADHF developed an AKI. This percentage is in accordance with other biomarker studies in ADHF [25, 26]. Of note, AKI was already present upon admission in 17% of patients with ADHF, whereas AKI developed during hospital stay in an additional 22% of patients. Beside the AKI-defining markers sCr and eGFR, urinary NGAL was associated with developing AKI. NGAL showed superior and satisfying diagnostic performance to detect AKI in comparison to the other renal markers.

In accordance with other studies evaluating candidate renal biomarkers in acute or chronic heart failure, [27, 28, 29, 30, 31] biomarker concentrations in the current study were lower than the proposed concentrations for AKI detection. Singer et al showed that NGAL is able to differentiate between pre-renal and renal AKI, with lower biomarker concentrations in pre-renal AKI [32, 33]. Therefore, in heart failure AKI might be related more to pre-renal causes like venous congestion [30, 34], hypotension, decreased trans-renal pressure gradient and decreased renal blood flow [35] than renal causes like large tubular damage [31]. The necessity of defining cut-offs in the heart failure setting seems to be important in establishing the new renal markers as cardiorenal biomarkers in the future. The current NGAL finding complements our previous data which have shown greater prognostic benefit of KIM-1 than NGAL in chronic heart failure [27]. In contrast to these observations, NGAL outperforms KIM-1 in diagnosing AKI in ADHF. These findings raise the possibility that different renal biomarkers may indicate different outcomes. Therefore, the different potential strengths of each of the markers should be investigated further.

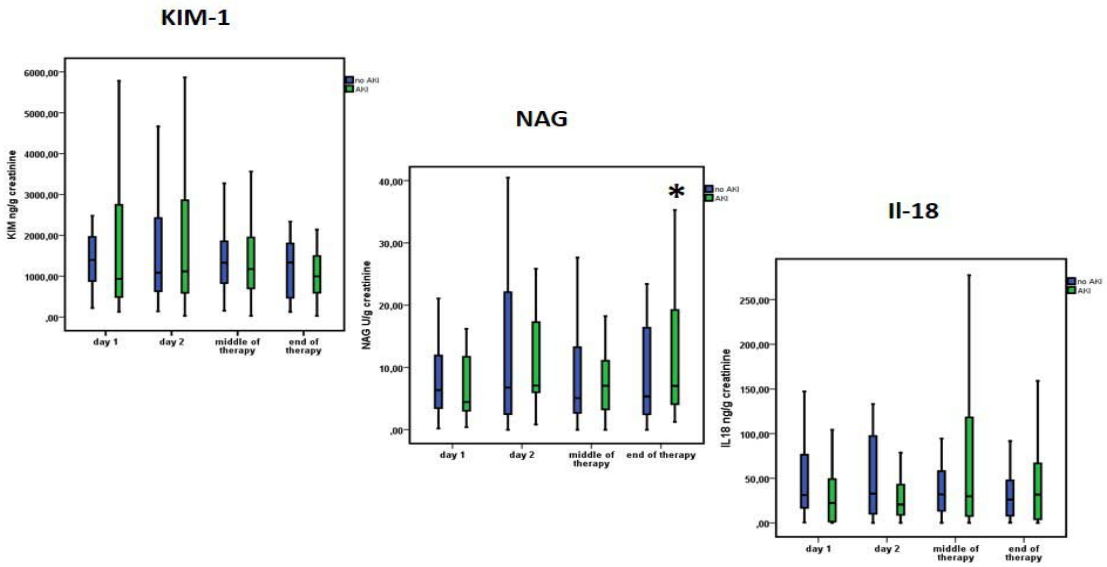

Figure 3: KIM-1, NAG and Il-18 concentrations at different time points: no AKI vs. AKI (* vs. middle of therapy $p < 0.05$).

Table 4: Binary logistic regression analysis regarding AKI development: NGAL at day 2.

	NGAL d2 >/< 23.8
age	0.92, p= 0.046
sex	n.s.
eGFR	0.92, p < 0.001
NYHA > 2	n.s.
marker	6.20, p= 0.039

Marker concentrations during recompensation in ADHF

The current study confirms and extends our current knowledge regarding the investigational renal markers in AKI. It confirms the superiority of NGAL for the diagnosis of AKI in ADHF and extends previous studies as it compares marker measurements at several sampling points for four candidate renal markers head-to-head and in comparison to established proteinuria markers and renal functional markers.

Protein, albumin and IgG decreased from day 1 to day 2 without significant change in marker concentration thereafter. These findings were only evident in patients without AKI, indicating that AKI is associated with ongoing protein excretion. However, the observed differences were not sufficient to propose albuminuria to detect AKI in the current collective.

Regarding urinary NGAL, the findings of the current study are in accordance with Collins et al, [36] with similar AUC value for detection of AKI. Also, the current study does not emphasize the initial NGAL value to be the best to detect AKI. The best predictive values were shown in the measurement collected the day prior to the creatinine rise, corresponding to the 12-24 hour value of Collins et al. Opposite to Dupont et al [29], who found only a minor rise in NGAL in patients with ADHF, the current study defined AKI not only as a relevant creatinine rise >0.3mg/dl compared to baseline sCr, but also compared to sCr values <= 3 months before hospitalization. Therefore, the current study identified 10 patients with preexisting AKI at hospital admission.

The other three candidate renal markers are not well investigated in ADHF [31, 33]. Verbrugge FH et al investigated three of the renal biomarkers (NGAL, KIM-1, Il-18) head-to-head, [31] but they measured the markers only once during the first 24 hours after admission due to ADHF. The main finding was a relatively weak correlation between these renal markers and AKI. The present study included patients during the first 6 hours after arrival at hospital and several measurements were performed. Also, the patients in the current study were older and the degree of chronic kidney disease was worse. This might explain these differences in the diagnostic performance of the markers.

The majority of trials regarding cardiorenal syndrome evaluated these markers in patients undergoing cardiac surgery, contrast nephropathy or renal transplantation [8, 37, 38, 39]. All those studies have in common, that the timing of renal injury was known. In ADHF, however, it is likely that many patients suffer from deterioration of renal function before hospital admission. Therefore it is not known whether kidney injury occurred before admission due to ADHF or after admission due to diuretic therapy or worsening ADHF. The current study was not able to display relevant marker differences between patients with AKI at admission and AKI developing after admission. This might be due to the low event rate in our relatively small cohort. Larger studies are needed to clarify these findings and the value of the different biomarkers in acute heart failure.

Conclusion

The current study investigated four tubular renal markers as potential biomarkers of the cardiorenal syndrome in acute decompensated heart failure. Particularly NGAL showed promising diagnostic performance and exceeded in diagnosing AKI, whereas NAG and KIM-1, albeit partly elevated, do not display sufficient diagnostic strength to detect AKI in ADHF.

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