ORIGINAL ARTICLE

Elevated urinary kidney injury molecule 1 at discharge strongly predicts early mortality following an episode of acute decompensated heart failure

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KEY WORDS

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EDITORIAL

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ABSTRACT

INTRODUCTION Hospitalization for acute decompensation of heart failure (ADHF) is a frequent event associated with long-term adverse effects. Prognosis is even worse if acute kidney injury (AKI) occurs during hospitalization.

OBJECTIVES The study aimed to determine whether kidney damage biomarkers neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), and interleukin 18 (IL-18) might predict AKI and have prognostic value in ADHF.

PATIENTS AND METHODS Serum NGAL on admission and urine NGAL, KIM-1, and IL-18 on discharge were determined in 187 ADHF patients enrolled in a prospective, observational, unblinded study. AKI was diagnosed using the Kidney Disease: Improving Global Outcomes criteria. Patients were followed for 12 months to record all-cause mortality.

RESULTS A total of 22% patients died during the follow-up, with 52.5% dying within 4 months after discharge. Serum NGAL (P <0.001), urine NGAL (P = 0.047), and urinary KIM-1 (P = 0.014) levels were significantly higher in the deceased patients at discharge. After adjustment for estimated glomerular filtration rate (eGFR), only urinary KIM-1 independently predicted mortality at month 4 (hazard ratio [HR], 3.166; 95% CI, 1.203–8.334; P = 0.020) and month 12 (HR, 1.969; 95% CI, 1.123–3.454; P = 0.018) in Cox regression models. In receiver operating characteristic (ROC) analysis urinary KIM-1 (area under the ROC curve [AUC] = 0.830) outperformed other markers of renal function. The Kaplan–Meier survival analysis showed KIM-1 predictive value as additive to that of AKI incidence and admission eGFR. Admission serum NGAL was higher in AKI patients (P ≤0.001) with a modest diagnostic performance (AUC = 0.667), below that of urea (AUC = 0.732), creatinine (AUC = 0.696), or cystatin C (AUC = 0.676).

CONCLUSIONS Discharge urinary KIM-1 was a strong and independent predictor of mortality, particularly during the most vulnerable period shortly after hospitalization. Admission serum NGAL was inferior to conventional renal function parameters in predicting AKI during ADHF.

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INTRODUCTION Acute decompensation of heart failure (ADHF) is a common cause of hospitalization in the elderly. Suffering an ADHF episode is linked to a higher risk of death in the 12 months following the index event. Over the last 20 years, the causes of death have shifted, with

WHAT'S NEW?

In a 12-month follow-up study of patients suffering from an acute decompensated heart failure (ADHF) episode, more than half of the fatalities happened in the first 4 months following discharge. We found that elevated relative urine kidney injury molecule 1 (KIM-1) level (μg/g creatinine) at discharge is a significant and independent predictor of increased mortality risk during the most susceptible time (4-month follow-up). The association was independent of previous renal function or N-terminal pro-brain natriuretic peptide levels and was additive to the risk conferred by acute kidney injury incidence. Urinary KIM-1 measurements in ADHF patients may be beneficial in identifying individuals at a higher risk of adverse outcomes and so requiring closer follow-up. Our finding differs from other studies showing a dissociation between renal function and tubular markers in that KIM-1 was measured in urine collected at the time of discharge when clinical stability had been achieved.

noncardiovascular events (primarily neoplasms, respiratory diseases, and infections) steadily increasing. Pump failure, ischemic events, and sudden death are the most common cardiovascular causes, still accounting for 43% of all deaths.[1] On the other hand, there is compelling evidence that concurrent renal disease plays an important role in determining ADHF prognosis. A cardiorenal syndrome (CRS) framework has been developed to aid understanding of the complex pathophysiological interrelationship between the heart and kidney disease. CRS type I, the most common of these syndromes, identifies the development of acute kidney injury (AKI) in the context of ADHF and has been linked to an increased mortality risk in ADHF patients.[2] AKI's effect is independent of previous renal disease (chronic kidney disease [CKD]), which is a well-known risk factor for all-cause mortality in heart failure.

Traditionally, AKI diagnosis has relied on changes in blood creatinine, which is not always effective in acute settings. This problem prompted the search for and subsequent identification of several molecular biomarkers of renal tubule damage, all of which have been thoroughly evaluated for their AKI diagnostic value.[3,4] Neutrophil-gelatinase associated lipocalin (NGAL)[5] and kidney injury molecule 1 (KIM-1)[6] were identified as being specifically released by the damaged renal tubule in animal models of kidney damage, and have demonstrated good sensitivity and specificity for AKI diagnosis in multiple clinical settings.[7,8] Molecules involved in the inflammation associated with renal function impairment, such as the proinflammatory cytokine interleukin 18 (IL-18) have also demonstrated some utility in diagnosing AKI in acute clinical conditions.[9] However, evidence on the clinical utility of renal tubule damage biomarkers in a complex setting of ADHF is still inconclusive. While most studies agree that renal tubule damage biomarkers offer poor AKI diagnostic value, they still hold promise as prognostic markers in ADHF.[10-13] Furthermore, it has not been sufficiently investigated whether individual biomarkers have a distinct ability to predict mortality at early or late time points following an ADHF episode.

The current study investigated the predictive usefulness of discharge NGAL plasma and urine levels, as well as KIM-1 and IL-18 urine levels, in patients hospitalized for ADHF. Because the fatality rate associated with ADHF hospitalization is higher in the first 4 months after the event, we focused on determining the biomarker the most effective at predicting mortality during that most susceptible period.

PATIENTS AND METHODS

Study design

This prospective, observational, unblinded study involved 204 patients enrolled consecutively (between February 2013 and January 2015), admitted to the internal medicine department of a tertiary teaching center for incident AHF or decompensated chronic HF (ADHF). A thorax radiological study and, in most cases, ecocardioscopy (covering lungs and cava veins) were part of the initial clinical assessment. The study included patients with both preserved and reduced left ventricular ejection fraction (LVEF). The patients with LVEF above 45% were included if the left ventricular hypertrophy and/or dilated left auricle was observed. Those with N-terminal pro-brain natriuretic peptide (NT-proBNP) levels above the age-adjusted cutoff were diagnosed with ADHF.[14] Advanced CKD (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m^2, calculated from Modification Of Diet In Renal Disease [MDRD] or Chronic Kidney Disease Epidemiology Collaboration formulas), neoplasia, refusal to consent, shortened life expectancy, or inotropic therapy were all exclusion criteria at the time of admission.

The study followed the Declaration of Helsinki's principles and was authorized by Aragón's Committee on Research Ethics (PI13/0119). All the participants gave their informed consent.

Clinical and laboratory data and study biomarkers

Clinical data were collected, and general laboratory panel was run on admission and every 2–3 days until discharge. Serum creatinine values and the MDRD-eGFR formula were used to estimate renal function in subsequent analysis. On admission and 24 hours before release, NT-proBNP (Roche Diagnostics, Mannheim, Germany) and cystatin C (Dade Behring, Marburg, Germany) were measured. Additional serum samples (designated as 's' in the acronym) were obtained, processed, and frozen at –80 °C until analysis for the assessment of the study biomarkers at admission ('adm' samples) and discharge ('dis' samples). Before discharge, a spot urine sample (designated as 'u' in the acronym) was collected, centrifuged, aliquoted, and kept frozen at –80 °C until analysis.

AKI was diagnosed during hospitalization using the Risk, Injury, Failure, Loss of kidney

function, and End-stage kidney disease (RIFLE) or the Acute Kidney Injury Network (AKIN) criteria (an increase in serum creatinine of ≥0.3 mg/dl or ≥50% over admission at any measurement during hospitalization).

Serum and urinary NGAL (sNGAL, uNGAL; DLCN20, R&D Systems Europe, Abingdon, United Kingdom) and urinary KIM-1 (uKIM-1; DKM100; R&D Systems Europe, Abingdon, United Kingdom) and IL-18 (uIL-18; 7620; MBL, Woburn, Massachusetts, United States) were quantified following the manufacturer's instructions. Concentration of biomarkers in biological fluids was calculated from the calibration curves using a 4-parameter logistic fitting. All of the patient samples were tested in duplicate. uNGALr (ng NGAL/mg Cr), uKIM-1r (ng KIM-1/mg Cr), uIL-18r (g IL-18/mg Cr) are the relative urinary biomarker excretion rates, which were estimated by dividing their urinary concentration by urinary creatinine.

Patient follow-up and end points Following discharge, follow-up visits were scheduled for months 1, 3, 6, and 12 after the hospitalization. Primary outcomes were all-cause mortality, HF rehospitalization, and the combined outcome. Duration of hospital stay and in-hospital mortality were secondary outcomes.

Statistical analysis Continuous data are given as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the variable normality assessed by the Kolmogorov–Smirnov test. When performing simple or multiple comparisons on parametric distributions, differences were examined using the *t* test or ANOVA. The frequency distribution of qualitative variables is provided as absolute value and percentage. The Mann–Whitney, Kruskal–Wallis, or χ^2 test was used to analyze differences in nonparametric distributions. The Pearson and Spearman tests were used to establish correlations, depending on normality. The Wilcoxon and Friedman tests were employed to test for differences between groups for nonparametric variables. Because missing data were considered to occur at random, no imputations were performed.

The predictive value of biomarkers and traditional clinical findings was compared using the receiver operator characteristic (ROC) curve analyses and the calculation of areas under the curve (AUC). Cutoff values were chosen according to Youden's *J* statistic (*J* = sensitivity + specificity – 1). To calculate cumulative survival, the event-free Kaplan–Meyer method with the long-rank test was used.

In univariable analysis, hazard ratios (HR) with a 95% CI were calculated to estimate the association of end points with biomarker levels. Cox regression proportional hazard models were used for multivariable analysis, which included variables that had previously showed univariable association at *P* below 0.1 or other clinical parameters that had previously showed a predictive value. Quantitative variables were transformed into standardized variables (ln X-mean/SD) for the univariable and multivariable analysis.

SPSS version 22.0 was used for all analyses (SPSS Inc, Chicago, Illinois, United States). The 95% CIs were given, and a *P* value of 0.05 was considered significant.

RESULTS

Clinical characteristics, acute kidney injury incidence, and mortality outcome The main clinical characteristics of the 204 patients admitted for ADHF in our cohort are summarized in TABLE 1. On admission, the mean eGFR ranged from 46.2 to 62.4 ml/min/1.73 m^2, depending on the formula used. Hypertensive cardiomyopathy (39.2%), ischemic cardiomyopathy (28.9%), and valvular heart disease (19.1%; 9.3% aortic, 7.2% mitral, 2.6% right valvulopathy) were the most common causes of HF. According to the MDRD formula, 85.2% of patients had an admission eGFR below 60 ml/min/1.73m^2; however, only 26.5% had previously been diagnosed with CKD.

According to the RIFLE criteria, 17.2% (n = 35) of patients had AKI. On the other hand, AKI was present in 24.5% (n = 50) of patients based on the AKIN classification (increase in SCr ≥0.3 mg/dl). Overall, 13.2% (n = 27) of patients met both criteria, while 28.4% (n = 58) met one of them. TABLE 1 compares clinical characteristics in patients with AKI (AKI+) and those who did not have AKI (non-AKI). Regardless of the formula used, the incidence of AKI was higher in patients with previously diagnosed CKD (*P* = 0.02), and was associated with worse renal function on admission. AKI was 3 to 4 times more common in the patients with admission eGFR below 60 ml/min/1.73 m^2 (*P* <0.001).

During their hospitalization, 5 patients (2.5%) died. A total of 40 deaths were recorded during the follow-up, with cumulative frequencies of 5.9%, 12.7%, and 22.1% in the first, fourth, and twelfth month following discharge, respectively. HF was the cause of death in 81% of all cases. Age (*P* = 0.001), lower admission eGFR (*P* = 0.003), longer hospitalization (*P* = 0.03), and higher blood levels of urea (*P* <0.001), creatinine (*P* = 0.03), NT-proBNP (*P* <0.001), and cystatin C (*P* = 0.01) on admission were all statistically associated with 12-month mortality.

As expected, AKI patients had a higher mortality rate, as 15.5% died in the hospital or during the first month of the follow-up. At month 12, AKI+ patients had an all-cause mortality rate of 44.8%, as compared with 15.06% in non-AKI patients. AKI was found in 54.2% of the deceased and 20.5% of the survivors (*P* <0.001). Most AKI-related deaths were caused by HF.

Urinary kidney injury molecule 1 is a strong and independent predictor of early mortality During the follow-up, 52.5% deaths in our cohort occurred within the first 4 months

TABLE 1 Clinical characteristics of patients on admission and acute kidney injury incidence

Characteristics	Total	AKI+	Non-AKI	*P* value
Demographics				
N (%)	204	146 (71.6)	58 (28.4)	–
Age, y	81 (76–85)	80.3 (74–83)	83.92 (81–89)	0.34
Male sex	103 (50.5)	75 (51.4)	28 (48.3)	0.69
Hospital stay, d	8 (7–13)	8.5 (7–14)	16.5 (9–27)	0.007[a]
NYHA				
NYHA Class I	10 (5.1)	10 (100)	0 (0)	0.002[a]
NYHA Class II	141 (71.9)	114 (81)	27 (19)	
NYHA Class III	45 (23.0)	27 (60)	18 (40)	
Clinical profile				
Vital signs on admission				
Heart rate, bpm	81 (70–99)	86 (70–98)	80 (62–93)	0.81
SBP, mm Hg	140 (43)	141 (43)	140 (39)	0.93
DBP, mm Hg	74 (19)	75 (18)	70 (20)	0.04[a]
LVEF, %	54 (24)	52 (23)	60 (27)	0.08
Peripheral edema	134 (66.7)	96 (66.7)	38 (66.7)	1.00
Jugular ingurgitation	115 (56)	66 (45.8)	37 (64.9)	0.03[a]
Comorbidities				
Ischemic cardiomyopathy	74 (37)	55 (38)	19 (32.8)	0.47
Hypertension	172 (85)	122 (84.7)	50 (84.2)	0.79
Valvular disease	37 (19)	26 (18.8)	11 (19.7)	0.41
Diabetes mellitus	80 (40)	58 (40.3)	22 (37.9)	0.76
Atrial fibrillation	118 (57.8)	87 (60.4)	31 (53.4)	0.36
CKD	54 (27)	32 (22.2)	22 (37.9)	0.02[a]
Chronic anemia	39 (19.3)	25 (17.4)	14 (24.1)	0.27
COPD	38 (19)	27 (18.8)	11 (19)	0.97
Medication at discharge				
β-Blockers	108 (56.3)	81 (57.9)	27 (51.9)	0.46
ACEIs/ARBs	147 (76.6)	110 (78.6)	37 (71.2)	0.65
Diuretics (furosemide, thiazides)	179 (93.2)	132 (94.3)	47 (90.4)	0.34
MRAs	64 (33.7)	45 (32.1)	19 (38)	0.45
Laboratory				
Hb, g/dl	12.2 (2.3)	12.3 (2.1)	12.3 (1.9)	0.52
Hematocrit, %	37.4 (8.5)	37.4 (8.8)	37.7 (7.9)	0.28
MCV, fl	91 (85.3–95.4)	93 (86–96)	91.3 (85–92)	0.48
RDW, %	15.7 (14.7–17.5)	15.4 (15–18)	15.5 (15–18)	0.28
BUN, g/l	0.6 (0.4–0.7)	0.50 (0.4–0.7)	0.65 (0.6–0.9)	<0.001[a]
Creatinine, mg/dl	1.1 (0.9–1.4)	1.06 (0.9–1.4)	1.54 (1.2–1.7)	<0.001[a]
eGFR-MDRD, ml/min/1.73 m^2	58.6 (40–72)	58.3 (43–72)	39.2 (32–55)	<0.001[a]
Uric acid, mg/dl	7.8 (2.7)	7.5 (2.3)	8.9 (4)	0.001[a]
Sodium, mEq/l	142 (140–144)	142.0 (140–144)	141.9 (139–144)	0.21
Potassium, mEq/l	4 (0.5)	3.9 (0.5)	4.1 (0.6)	0.30
GGT, U/l	43 (23.5–84)	47 (25–76)	42 (25–148)	0.78
Total cholesterol, mg/dl	145 (121–161)	136 (121–157)	128 (112–147)	0.22
Triglycerides, mg/dl	88 (76–118)	92.5 (78–118)	78.5 (71–91)	0.72
Total protein, g/dl	6.4 (0.8)	6.4 (0.6)	6.3 (0.7)	0.08
Albumin, g/dl	3.2 (0.5)	3.2 (0.5)	3.1 (0.7)	0.02[a]
NT-proBNP, pg/ml	3306 (1609–6997)	3459 (1669–8101)	3576 (2221–7522)	0.15
Cystatin C, mg/l	1.45 (1.2–1.8)	1.48 (1.2–2.0)	2.00 (1.8–2.1)	<0.001[a]

Values are shown as mean (SD) for parametric quantitative variables and median (Q1–Q3) for nonparametric variables, and as net number and percentage for qualitative variables.

SI conversion factors: to convert hemoglobin to mmol/l, multiply by 0.1562, creatinine to mmol/l multiply by 0.0884, uric acid to mmol/l multiply by 0.0595, sodium or potassium to mmol/l multiply by 1, cholesterol to mmol/l multiply by 0.0259, NT-proBNP to pmol/l multiply by 0.1176, and cystatin C to umol/l multiply by 0.0749.

a Significant *P* values

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR-MDRD, estimated glomerular filtration rate by Modification of Diet in Renal Disease study formula; GGT, gamma-glutamyl transpeptidase; Hb, hemoglobin; LVEF, left ventricular ejection fraction; MCV, mean corpuscular volume; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal fragment of pro-brain natriuretic peptide; NYHA, New York Heart Association; RDW, red cell distribution width; SBP, systolic blood pressure

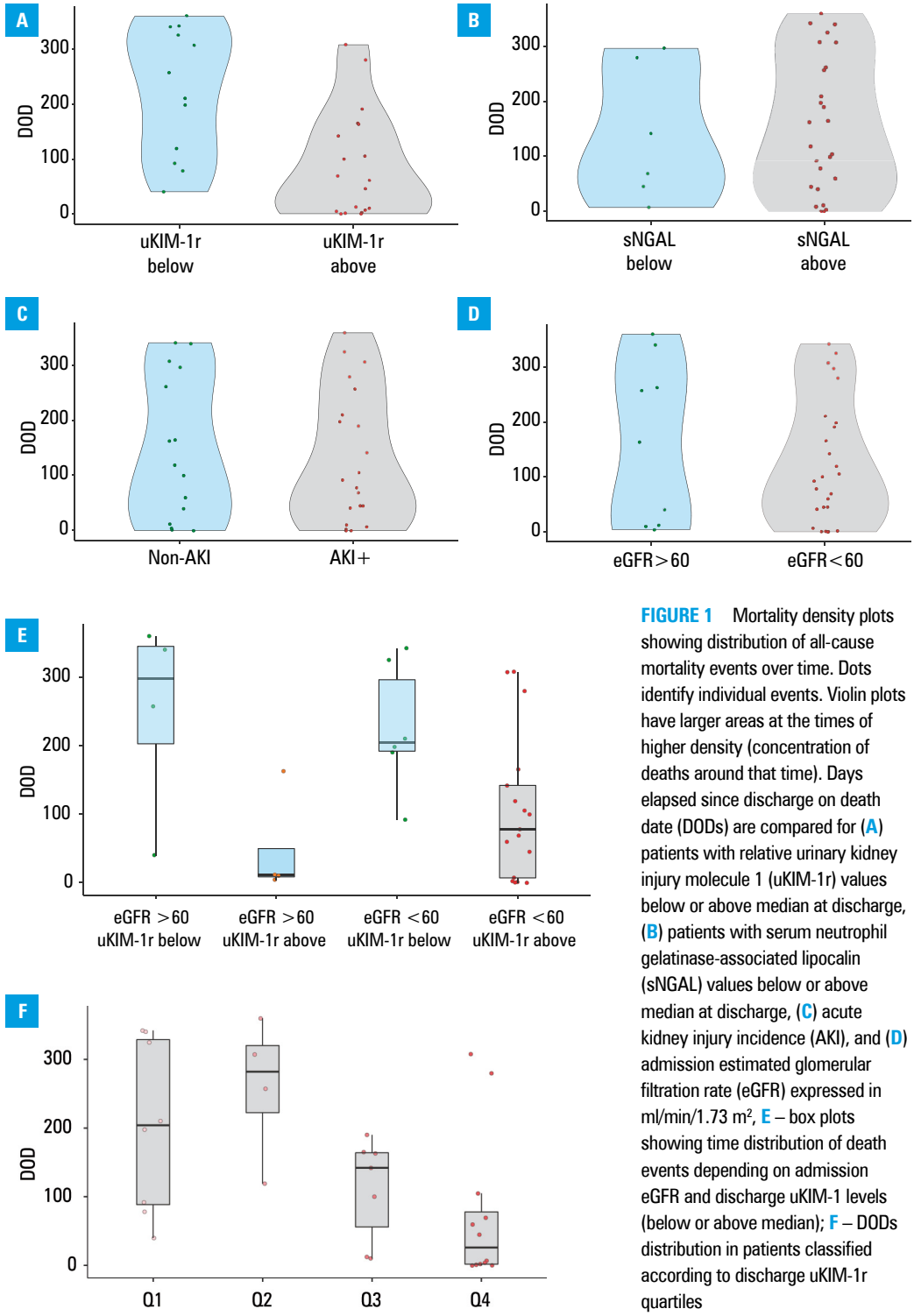

FIGURE 1 Mortality density plots showing distribution of all-cause mortality events over time. Dots identify individual events. Violin plots have larger areas at the times of higher density (concentration of deaths around that time). Days elapsed since discharge on death date (DODs) are compared for (**A**) patients with relative urinary kidney injury molecule 1 (uKIM-1r) values below or above median at discharge, (**B**) patients with serum neutrophil gelatinase-associated lipocalin (sNGAL) values below or above median at discharge, (**C**) acute kidney injury incidence (AKI), and (**D**) admission estimated glomerular filtration rate (eGFR) expressed in ml/min/1.73 m^2, **E** – box plots showing time distribution of death events depending on admission eGFR and discharge uKIM-1 levels (below or above median); **F** – DODs distribution in patients classified according to discharge uKIM-1r quartiles

after discharge. Associations between mortality time distribution and serum biomarker levels (sNGAL: ng/ml serum at admission and discharge) or urine (uNGALr, uKIM-1r, and uIL--18r: ng/mg creatinine in discharge urine) were analyzed. The group with uKIM-1r above the median had a noticeable mortality concentration in the first 4 months after the discharge (71.4%, FIGURE 1A). This distribution was strikingly different from the more even distribution observed for other markers, as shown for discharge sNGAL (FIGURE 1B). The incidence of AKI or previous CKD had no effect on the distribution of deaths (FIGURE 1C and 1D). Higher uKIM1r levels at discharge identified patients at a risk of dying prematurely, even for those in the low eGFR (<60 ml/min/1.73 m^2) group (FIGURE 1E). Interestingly, date of death (DOD, or the number of days from discharge to death) appeared to be dependent on KIM-1 relative urine concentrations (FIGURE 1F).

Hence, median uKIM-1r values, but not those of other biomarkers, were associated with higher mortality in the first month (P = 0.007; Supplementary material, *Table S1*). The patients with uKIM-1r levels above the median also tended to

TABLE 2 Operational characteristics for tubular biomarkers value in predicting mortality

Parameter	AUC 1 month	Cutoff	Sens, %	Spec, %	AUC 4 months	Cutoff	Sens, %	Spec, %	AUC 12 months	Cutoff	Sens, %	Spec, %
sUrea, g/l	0.632	0.62	67	61	0.688	0.63	69	63	0.713	0.56	69	61
sCr, mg/dl	0.546	1.14	67	49	0.658	1.22	69	62	0.683	1.2	69	63
sCystatin C, mg/l	0.727	1.6	83	60	0.762	1.55	84.6	60	0.735	1.5	81	61
Admission sNGAL, ng/ml	0.760	190	83	64	0.700	190	77	65	0.704	174	77	61
Discharge sNGAL, ng/ml	0.731	243	83	73	0.715	214	77	62	0.752[a]	225[a]	77[a]	73[a]
Relative uNGAL, µg/g Cr	0.721	21.3	83	62	0.698	32.8	70	60	0.538	20.5	54	60
Relative uKIM-1, µg/g Cr	0.830[a]	1.12[a]	83[a]	67[a]	0.766[a]	1.77[a]	77[a]	60[a]	0.587	0.98	58	57
Relative uIL-18, ng/g Cr	0.511	8.1	67	50	0.542	16.65	54	60	0.496	8.1	58	51

Data from 138 patients were analyzed for all variables.

a The highest AUC for each analysis

SI conversion factors: to convert urea to mol/l, multiply by 0.0167, creatinine to mmol/l multiply by 0.0884, Cystatin C to umol/l multiply by 0.0749, NGAL to nmol/l multiply by 0.0417, relative NGAL to nmol/mol Cr multiply by 4.7133, relative KIM-1 to nmol/mol Cr multiply by 1.8853, relative IL-18 to pmol/mol Cr multiply by 6.5767.

Abbreviations: AUC, area under the curve; Cr, creatinine; IL-18, interleukin 18; KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatin associated lipocalin; s, serum; Sens, sensitivity; Spec, specificity; u, urinary

have higher 4-month mortality rates ($P = 0.06$), but not when the entire 12-month follow-up period was considered ($P = 0.32$).

A cutoff concentration of 1.12 µg/g Cr uKIM-1r at discharge predicted mortality at 1 month (AUC = 0.830, 83% sensitivity; 67% specificity; TABLE 2) outperforming serum urea, creatinine, and cystatin C. At month 4, discharge uKIM-1r still had a high predictive power for mortality (Supplementary material, *Figure S1A*). On the other hand, uKIM-1r levels at discharge did not predict 12-month mortality (TABLE 2, Supplementary material, *Figure S1B*).

Survival analysis (FIGURE 2) revealed that discharge levels of uKIM-1r (P value in log rank = 0.03; FIGURE 2A) and sNGAL (P value in log rank <0.001; data not shown) had a positive predictive value of 4-month (120 days) mortality. Addition of uKIM-1r to discharge sNGAL, AKI incidence, or low eGFR significantly increased the risk of death at 120 days (FIGURE 2B–2D). At 365 days, the additive effects of uKIM-1r to AKI incidence or low eGFR were preserved (FIGURE 3A and 3B), despite the fact that uKIM-1r did not show discriminative value on its own (Supplementary material, *Figure S2D*).

A regression model was built that included pathophysiologally relevant variables having shown positive correlation with 4-month mortality in univariable analysis. At month 4, the only independent risk factors for all-cause mortality were admission NT-proBNP ($P = 0.01$) and discharge uKIM-1r ($P = 0.02$) (TABLE 3).

Long-term neutrophil gelatinase-associated lipocalin prognostic value is associated with renal function

Neither serum nor urinary NGAL values were associated with mortality rates at month 1. Serum NGAL at admission ($P = 0.04$) or discharge (P <0.001) was, on the other hand, positively associated with 12-month mortality, showing a contrary trend to uKIM-1r (Supplementary material, *Table S1*). Relative urinary NGAL or IL-18r levels were not associated with mortality during any of the follow-up periods (Supplementary material, *Table S1*; biomarker concentration distributions are shown in Supplementary material, *Table S2*).

In ROC analysis (TABLE 2, Supplementary material, *Figure S1B*) or the Kaplan–Meier analysis (log rank P <0.001; Supplementary material, *Figure S2*), discharge sNGAL displayed a strong predictive value for 12-month mortality, consistently outperforming all other markers. However, after adjusting for renal function (serum creatinine, serum cystatin C) in a multivariable regression model, discharge sNGAL lost its predictive value for 12-month mortality (TABLE 4). Age (HR, 2.366; $P = 0.02$), NT-proBNP (HR, 2.468; $P = 0.001$), AKI (HR, 3.017; $P = 0.01$), and uKIM-1r (HR, 1.833; $P = 0.02$) were all associated with significant independent risk.

During the 12-month follow-up, however, serum NGAL at discharge was the only positive independent predictor of the outcome of HF readmission (Supplementary material, *Table S3*) or the combined outcome with mortality (Supplementary material, *Table S4*) (HR, 1.511 and HR, 1.473, respectively), even after adjusting for renal function. When the fourth month's outcomes were analyzed, none of the markers under study had a predictive value. On month 12, NT-proBNP was only significant for the combined output. Interestingly, the patients with higher urinary KIM-1 at discharge tended to have a lower risk of HF rehospitalization, but this trend did not reach statistical significance.

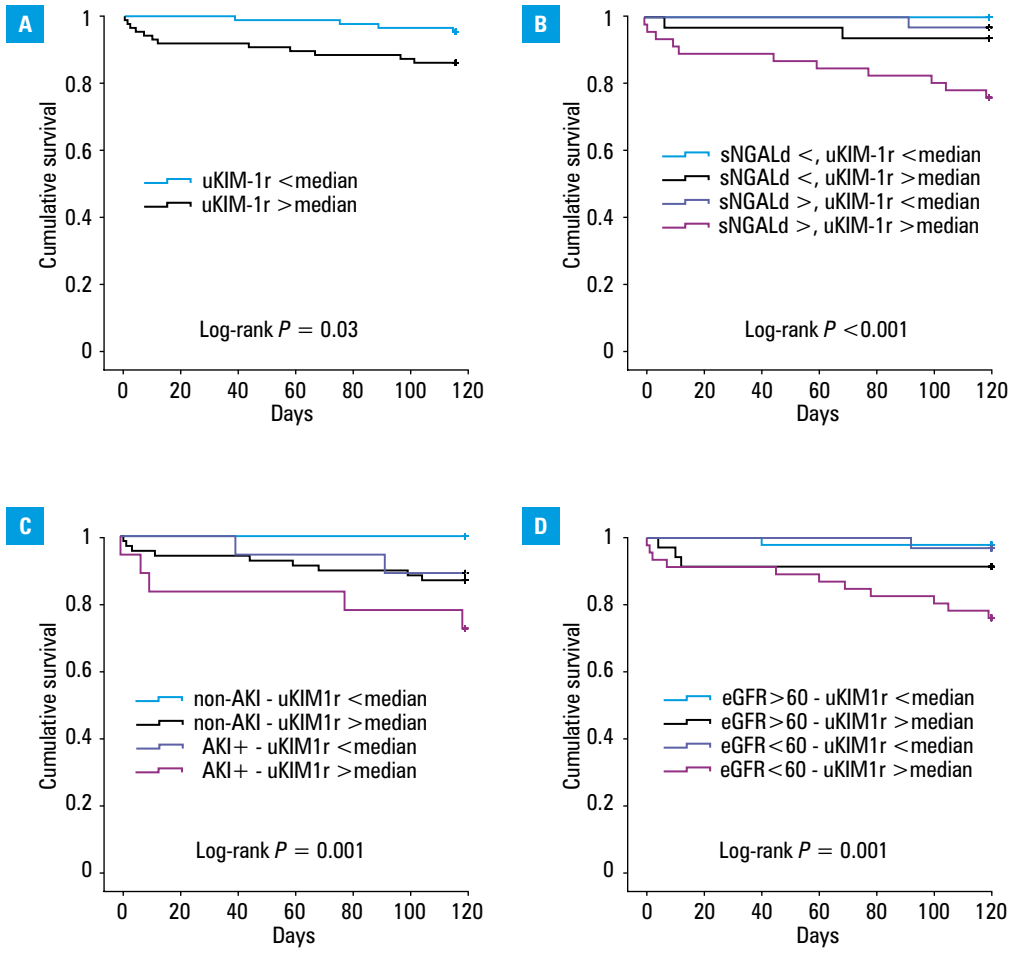

FIGURE 2 The Kaplan–Meier curves were plotted to analyze 4-month survival to the all-cause mortality outcome. Association was investigated for (**A**) relative urinary kidney injury molecule 1 (uKIM-1r) values at discharge, (**B**) serum neutrophil gelatinase-associated lipocalin at discharge (sNGALd), (**C**) acute kidney injury incidence (AKI), and (**D**) admission estimated glomerular filtration rate (eGFR)

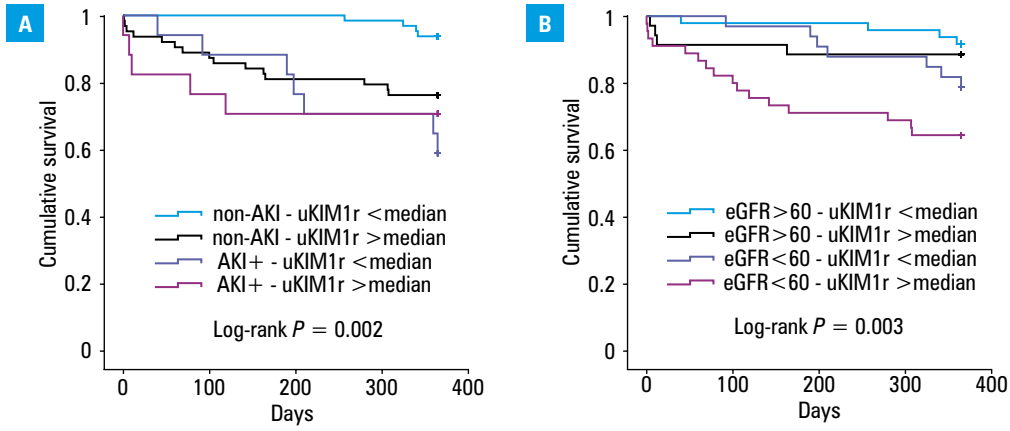

FIGURE 3 The Kaplan–Meier curves were plotted to analyze 12-month survival to the all-cause mortality outcome. Association was investigated for the combination of relative urinary kidney injury molecule 1 (uKIM-1r) values at discharge with (**A**) acute kidney injury (AKI) incidence and (**B**) admission estimated glomerular filtration rate (eGFR)

Renal tubule damage biomarkers do not diagnose acute kidney injury Serum NGAL levels in AKI+ patients were significantly higher at both admission (P <0.001) and discharge (P = 0.001, Supplementary material, *Table S5*). Serum NGAL, on the other hand, was a poorer predictor of AKI than blood urea but as good as cystatin C and creatinine (Supplementary material, *Table S5*; ROC curves shown as Supplementary material, *Figure S3*). Serum NGAL levels were found to negatively correlate with eGFR (P <0.001) and positively with creatinine, urea, and cystatin C (all P <0.001; Supplementary material, *Table S6*). Serum concentration of NGAL depended on eGFR at both admission and discharge (Supplementary material, *Table S7*).

TABLE 3 Cox regression analysis: prognostic values for 4-month all-cause mortality

Parameter	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	0.970	0.394–2.387	0.95	–	–	–
Age	1.546	0.843–2.837	0.16	–	–	–
Hospital stay, d	2.011	1.352–2.992	0.001[a]	–	–	–
LVEF <50%	0.368	0.138–0.980	0.045[a]	0.391	0.112–1.369	0.14
CKD	1.313	0.499–3.453	0.58	–	–	–
AKI	4.034	1.622–10.003	0.003[a]	1.042	0.270–4.024	0.95
Anemia	2.873	1.130–7.299	0.03[a]	1.073	0.306–3.757	0.91
Hematocrit	0.783	0.502–1.220	0.28	–	–	–
RDW	1.068	0.727–1.568	0.74	–	–	–
Urea	1.821	1.158–2.862	0.009[a]	1.492	0.779–2.856	0.23
Creatinine	1.400	0.991–2.150	0.12	–	–	–
Sodium	0.817	0.531–1.257	0.36	–	–	–
Albumin	0.564	0.376–0.874	0.006[a]	0.745	0.381–1.458	0.39
NT-proBNP	2.320	1.511–3.561	<0.001[a]	2.913	1.264–6.714	0.01[a]
CysC adm	1.642	0.999–2.700	0.05	–	–	–
Adm sNGAL	1.768	0.934–3.345	0.08	–	–	–
Dis sNGAL	1.915	1.020–3.593	0.043[a]	1.525	0.715–3.252	0.28
Urine creatinine	0.750	0.468–1.204	0.23	–	–	–
Relative uNGAL	1.777	1.025–3.082	0.04[a]	1.675	0.862–3.253	0.13
Relative uKIM-1	2.2935	1.586–5.432	0.001[a]	3.241	1.203–8.728	0.02[a]
Relative uIL-18	1.262	0.783–2.033	0.34	–	–	–

Data from 87 patients were analyzed for all variables. Quantitative variables were transformed into standardized variables (ln X-mean/SD) for the univariable and multivariable analysis.

a Variables significant (P <0.05) in the univariable or multivariable Cox regression analysis

Abbreviations: Adm, admission; CysC, cystatin C; Dis, discharge; HR, hazard ratio; others, see TABLES 1 and 2

The relative urinary concentrations of KIM-1 (uKIM-1r) in AKI+ patients were significantly higher than in the non-AKI group (P = 0.006; Supplementary material, *Table S5*). However, AKI incidence was not higher in the patient group with uKIM-1r above mean. Accordingly, uKIM-1r had a low AKI diagnostic value in ROC analysis (Supplementary material, *Table S5*, Supplementary material, *Figure S3*).

There were no differences in uNGALr or uIL-18r related to AKI incidence (Supplementary material, *Table S5* and *Figure S3*). None of the urinary biomarkers were associated with a history of CKD, and only uNGALr was associated with eGFR (Supplementary material, *Table S6*).

DISCUSSION Renal tubule damage biomarkers were measured in serum and urine of the patients hospitalized for ADHF to evaluate their ability to predict AKI incidence and their prognostic value for all-cause mortality. Our findings unveiled a hitherto unknown ability of discharge urine KIM-1 levels to predict mortality during the early follow-up period accounting for the largest fraction of fatalities.

Approximately one-third of the patients in our cohort suffered from AKI during hospitalization. Several studies have reported that higher serum NGAL levels independently predict worsening of renal function or AKI, defined as a rise in serum creatinine from 0.3 mg/dl onwards or above 50% over admission values throughout hospitalization.[15-19] In GISSI-HF trial, a prospective study of a large chronic heart failure (CHF) cohort,[20] NGAL also predicted worsening of renal function. Our results, however, are consistent with those of more recent and larger cohort studies[21-25] that show poor or none AKI diagnostic value for serum NGAL. Although admission serum NGAL levels were higher in AKI+ patients, they did not outperform urea, serum creatinine or cystatin C in predicting AKI. A similar finding was obtained in AKINESIS (Acute Kidney Injury Neutrophil Gelatinase-Associated Lipocalin [NGAL] Evaluation of Symptomatic Heart Failure Study),[26] a multicenter, prospective, observational cohort study that looked specifically into NGAL's ability to predict AKI in ADHF patients (n = 911). An addition of peak plasma NGAL to renal function markers improved the prediction of a combined end point including AKI and the need for renal-replacement therapy. However, as in our cohort, admission plasma NGAL did not outperform creatinine in predicting AKI (0.625 [95% CI, 0.554 to 0.695] vs 0.631 [95% CI, 0.552 to 0.711]). As a result, it was concluded that blood NGAL measurements

TABLE 4 Cox regression analysis: prognostic values for 12-month all-cause mortality

Parameter	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	1.137	0.615–2.100	0.68	–	–	–
Age	2.166	1.289–3.639	0.003[a]	2.366	1.164–4.810	0.02[a]
Hospital stay, d	1.486	1.086–2.032	0.01[a]	0.871	0.487–1.557	0.64
LVEF <50%	0.597	0.318–1.121	0.11	–	–	–
CKD	2.221	1.186–4.158	0.01[a]	1.791	0.714–4.491	0.21
AKI	4.041	2.092–7.807	<0.001[a]	3.017	1.271–7.162	0.01[a]
Anemia	1.651	0.807–3.378	0.17	–	–	–
Hematocrit	0.722	0.525–0.993	0.045[a]	0.865	0.526–1.420	0.57
RDW	1.258	1.030–1.537	0.02[a]	1.229	0.888–1.699	0.21
Urea	2.033	1.466–2.820	<0.001[a]	1.424	0.795–2.550	0.23
Creatinine	1.543	1.141–2.085	0.005[a]	0.637	0.315–1.288	0.21
Sodium	0.796	0.582–1.088	0.15	–	–	–
Albumin	0.667	0.490–0.908	0.01[a]	1.026	0.658–1.600	0.91
NT-proBNP	2.114	1.478–3.024	<0.001[a]	2.468	1.427–4.271	0.001[a]
CysC adm	1.778	1.235–2.559	0.002[a]	1.562	0.676–3.606	0.30
Adm sNGAL	1.387	0.960–2.002	0.08	1.314	0.572–3.020	0.52
Dis sNGAL	1.665	1.101–2.517	0.02[a]	1.442	0.603–3.448	0.44
Urine creatinine	0.628	0.452–0.871	0.005[a]	0.843	0.488–1.454	0.54
Relative uNGAL	1.619	1.097–2.390	0.02[a]	1.256	0.729–2.162	0.41
Relative uKIM-1	1.510	1.006–2.266	0.047[a]	1.833	1.079–3.116	0.02[a]
Relative uIL-18	1.322	0.942–1.854	0.11	–	–	–

Data from 187 patients were analyzed for all variables. Quantitative variables were transformed into standardized variables (ln X-mean/SD) for the univariable and multivariable analysis.

a Variables significant (P <0.05) in the univariable or multivariable Cox regression analysis

Abbreviations: see TABLES 1, 2, and 3

do not add enough clinical value to warrant their routine use in the ADHF scenario. A recent analysis of urine NGAL levels in the AKINESIS cohort yielded similar results.[27] The fact that serum NGAL concentrations are primarily determined by renal function would explain NGAL's poor predictive ability in AKI,[25,28] as demonstrated also by our findings. On the other hand, intensive diuretic therapy during the active decongestion phase appears to dissociate changes in serum and urine NGAL from those in renal function markers. Such phenomenon confounds the assessment of tubular markers' AKI diagnostic and prognostic abilities during the active decongestion phase.[22,24,29,30]

We hypothesized that elevated tubule damage markers at discharge, which represent residual tubular cell stress caused by pathogenic mechanisms (eg, neurohumoral activation) or therapeutic efforts, are independent factors related to worse outcomes following an ADHF episode. Elevated urine NGAL has previously been linked to poorer outcomes in a variety of clinical settings, including CHF (GISSI-HF study)[31,32] and CKD (CRIC study).[33] Increased urine NGAL also appears to be a mortality risk factor in the elderly.[34,35] Most studies in ADHF patients show a positive correlation between elevated blood or urine NGAL during ADHF and worse outcomes (HR, 1.2–3.39), which would be irrespective of baseline renal function. Urine NGAL has been identified as an independent risk factor for all-cause mortality[13,15,34,36,37] and combined end points,[16,17,38] both short-term[16,17,36,38] or long-term[13,15,19,23,34,37] follow-up. In a recent extension of the AKINESIS study, admission serum and urine NGAL had a modest prognostic value in ROC analysis for the composite end point (death, HF hospitalization, and renal replacement therapy) at 30 and 60 days. Serum NGAL had a higher predictive capacity than urine NGAL, but not superior to that of serum creatinine. Only serum NGAL remained an independent predictor of 30-day mortality in adjusted models, performing better in individuals with low eGFR.[39] On the other hand, several studies found that NGAL had little prognostic value in the setting of acute[18,40] or chronic HF.[28,41] It has recently been demonstrated that measuring tubular markers during the active decongestion phase diminishes their prognostic value.[22,29,30] The time of measurement also appears to impact the predictive usefulness of other tubular function markers.[42] However, our study focused on biomarker levels at discharge, when decongestion was achieved and patients were clinically stable. We found discharge serum

NGAL associated with long-term mortality. However, it lost significance after adjusting for eGFR, a well-known predictor of worse outcomes in HF, suggesting that serum NGAL levels depend on renal function. Analysis of a prognostic value of serum NGAL may be further confounded by NGAL involvement in a myriad of systemic and organ pathological processes, ranging from inflammation to cancer, prevalent in the aged population where ADHF is prominent. Too many factors influence serum and urine NGAL concentrations in ADHF patients, precluding its use in everyday practice.

However, because KIM-1 appears to be produced solely by the kidney, KIM-1 urinary excretion should provide more precise information regarding renal tubular responses to stressors and insults. Urine KIM-1 has been linked to higher mortality and other adverse outcomes in the elderly,[43] CHF[12,31,44] or CKD[33] patients, generally in a eGFR-independent manner. Our study is the first to show that elevated urine KIM-1 levels at discharge are an independent factor contributing to a greater all-cause mortality risk in ADHF patients. There have been few studies on KIM-1 prognostic value in ADHF and the results have been conflicting. An early study in 83 ADHF patients indicated that urine IL-18, but not NGAL or KIM-1, had prognostic value at 7-month follow-up. None of the biomarkers correlated with eGFR.[45] In the ASCEND--HF[46] cohort (n = 874), after adjusting for standard indices of kidney function, baseline, 48- or 72-hour in-hospital circulating KIM-1 levels were not associated with adverse clinical outcomes in 180-day follow-up. Increased KIM-1 levels in 30-day follow-up, on the other hand, were found to be independently associated with higher 180-day mortality.[46] This finding further emphasizes the need for assessing the prognostic value of tubular markers at the appropriate time. In another study on 120 patients, Emmens et al[47] found that plasma KIM-1 predicted HF rehospitalization, but not 6- or 12-month mortality. Sokolski et al[19] investigated the association between urinary KIM-1 and all-cause mortality in 132 ADHF patients who were followed for 12 months. KIM-1 was not found to be an independent predictor of long-term mortality, although it was able to identify true worsening of renal function during hospitalization.[19] It is worth noting that our study is the first to investigate KIM-1 prognostic value for early mortality (1–4 months), which does not rule out the possibility that additional differences in clinical population, study design, or biomarker assessment contributed to the discrepancy.

The most clinically relevant finding of our study is the demonstration that urinary KIM-1 uniquely identifies patients at risk of dying during the most vulnerable period (1–4 months following discharge), regardless of renal function or cardiovascular status (NT-proBNP). The elevation in urinary KIM-1 might represent residual tubular cell stress, which has been recently associated with worse acute outcomes in ADHF.[48] Furthermore, the risk associated with elevated discharge uKIM-1 was additive to that associated with elevated discharge sNGAL, AKI incidence, or low renal function at admission. In patients not undergoing AKI during the ADHF episode, for example, the addition of sNGAL or uKIM-1 allowed for the detection of a subgroup at an elevated mortality risk. Combinations of clinical and biochemical biomarkers have been shown to improve diagnostic and prognostic power in acute or chronic HF.[12,13,23,32,35,37,38,46,49] Such compound indexes combining a few markers are significantly more useful than individual markers, especially if they provide a more comprehensive examination of diverse pathophysiological mechanisms.[40,50] Therefore, urinary discharge KIM-1, alone or in combination, adds substantial value to the prediction of death during the most vulnerable time following ADHF. This finding deserves additional validation in larger size studies aimed at developing compound panels for predicting worse evolution following an ADHF episode.

Limitations This is a moderately sized, single-center study with a limited number of events. We had little control over the interval between the onset of clinical decompensation and ward admission, making it difficult to estimate baseline values and interpret biomarker kinetics. The patients diagnosed with ischemic heart disease in the emergency department were more likely to be admitted to the cardiology division, introducing some bias in our cohort demographics. To decrease the patient heterogeneity and focus on the patients who might benefit from more frequent follow-up, we set eGFR below 30 ml/min/1.73 m^2 as an exclusion criterion. As a result, our findings may not be applicable to patients at the worse stage of renal dysfunction.

The patients received diuretics in accordance with standard care guidelines, but no individual records of total diuretic dosing during active decongestive treatment are available. Intensive diuretic therapy has been shown to confound the interpretation of changes in tubular damage biomarkers.[24,50] However, in our study the biomarkers were analyzed before intensive decongestion (admission), or once clinical stability had been achieved and the patients were on standard oral diuretic dosage (discharge). We measured experimental biomarkers using nonstandardized assay platforms, which have been effectively used in the past.

Conclusions Urine NGAL and IL-18 are of little or no utility in diagnosing AKI or predicting outcome in the setting of ADHF. Although admission serum NGAL can identify AKI during an episode of ADHF, it is not a better predictor of AKI than traditional renal function markers. When renal function is considered, discharge serum

NGAL does not provide useful predictive information. However, regardless of renal function, AKI incidence, or cardiovascular status, elevated urine KIM-1 at discharge identifies a subset of patients who are at an increased risk of mortality in the first few months following the discharge. As a result, urine KIM-1 should be included in biomarker panels or compound scores that provide clinical recommendations early in the ADHF follow-up process.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONTRIBUTION STATEMENT CJ-L, IG-L, and JIP-C conceived the concept of the study. JR-G, MS-M, AS, and PI contributed to the design of the research. All authors were involved in data collection. CJ-L, IG-L, and JIP-C analyzed the data. IG and JIP-C coordinated funding for the project. CJ-L, IG-L, and JIP-C prepared the original draft. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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