Supplementary material

Josa-Laorden C, Rubio-Gracia J, Sánchez-Marteles M, et al. Elevated urinary kidney injury molecule 1 at discharge strongly predicts early mortality following an episode of acute decompensated heart failure. Pol Arch Intern Med. 2022; 132: 16284. doi:10.20452/pamw.16284

Supplementary Figures

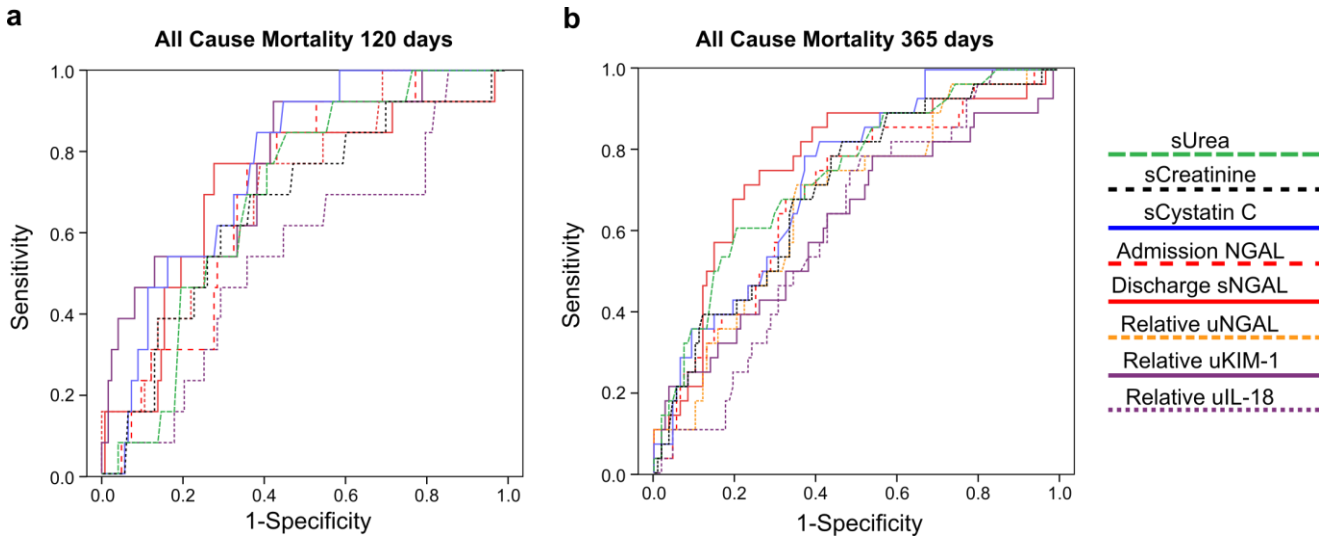

Figure S1. ROC analysis of the predictive value of renal damage biomarkers for 4 (a) and 12-month (b) all-cause mortality (ACM). ROC curves were analyzed for the five biomarkers under study and compared to markers of renal function.

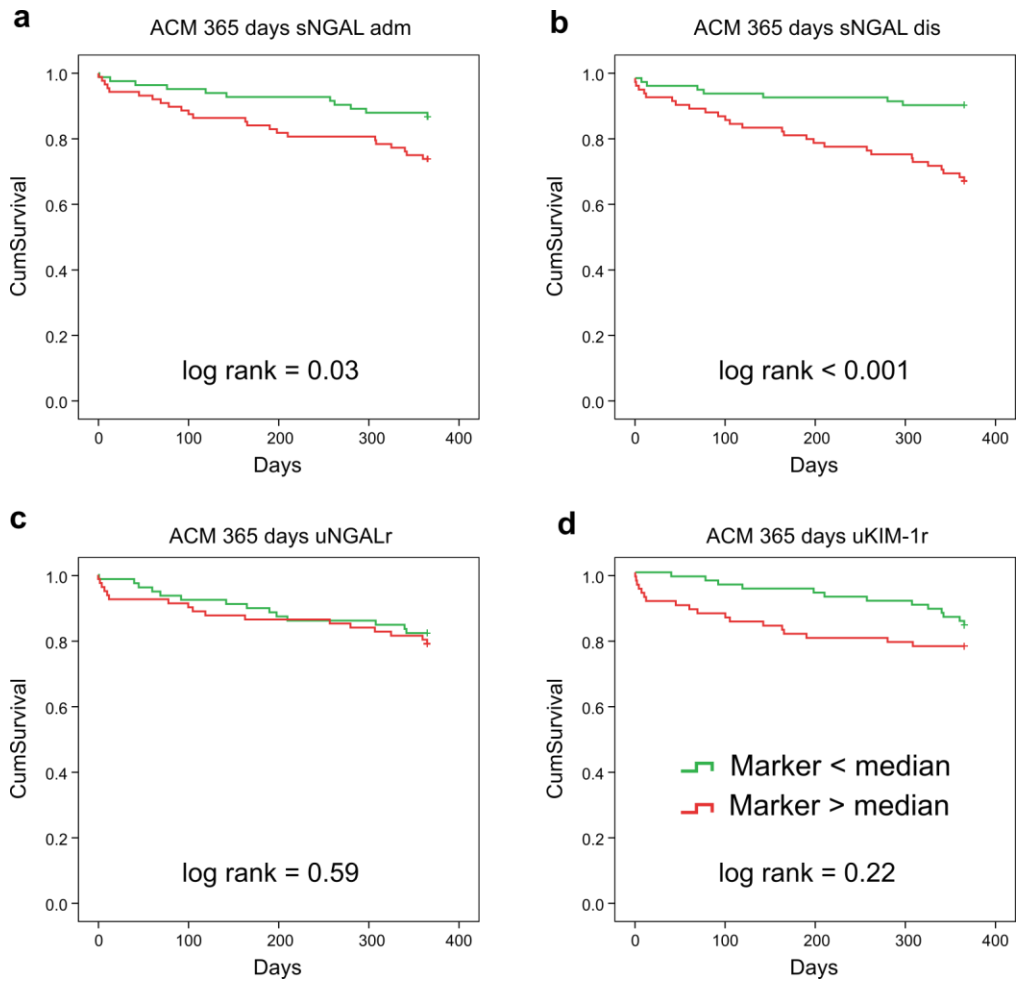

Figure S2. Kaplan-Meier survival curves for all-cause mortality (ACM) during the entire follow-up period (365 days). For each biomarker, cumulative survival was compared for patients above (red trace) or below (green trace) the median. Serum NGAL, both on admission (a) and discharge (b), was significantly associated with higher mortality. Urinary markers were normalized for urinary creatinine.

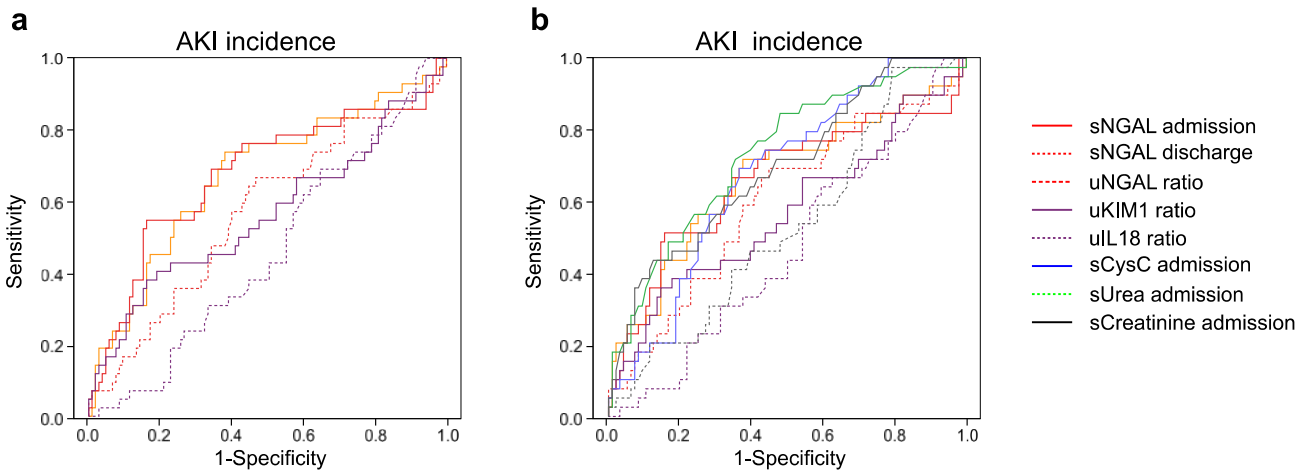

Figure S3: ROC analysis for prediction of AKI incidence in patients hospitalized for acute decompensated heart failure.

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Table S1. Analysis of mortality at 1, 4, and 12 months by levels of tubular damage markers

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Table S1. Analysis of mortality at 1, 4, and 12 months by levels of tubular damage markers

		1-month ACM	*P*	4-month ACM	*P*	12-month ACM	*P*
Admission sNGAL	≤ median	2 (2.4)	0.45	5 (6.0)	0.13	11 (13.3)	**0.04**
	> median	5 (5.7)		12 (13.6)		23 (26.1)	
Discharge sNGAL	≤ median	2 (2.4)	0.443	4 (4.7)	**0.04**	7 (8.2)	**<0.001**
	> median	5 (5.8)		13 (15.1)		27 (31.4)	
Relative uNGAL	≤ median	1 (1.3)	0.12	6 (7.5)	0.43	15 (18.8)	0.84
	> median	6 (7.4)		10 (12.3)		17 (21.0)	
Relative uKIM-1	≤ median	0 (0)	**0.007**	4 (4.9)	0.06	13 (16.0)	0.32
	> median	7 (8.8)		12 (14.8)		19 (23.5)	
Relative uIL-18	≤ median	4 (5.1)	0.72	10 (12.7)	0.31	17 (21.5)	0.70
	> median	3 (3.8)		6 (7.5)		15 (18.8)	

Values are shown as n (%).

Abbreviatures: ACM, all-cause mortality; NGAL, neutrophil gelatin associated lipocalin; KIM-1, kidney injury molecule 1; IL-18, interleukine-18.

Fisher's Exact Tests, significant differences (2-sided, P<0.05) are shown in bold.

Table S2: Biomarkers levels and primary outcome all-cause mortality on month 12

	Alive	Dead	*P*
Admission sNGAL, ng/mL	156.5 (117-219)	213.9 (175-270)	**0.04**
Discharge sNGAL, ng/mL	176.6 (126-230)	269.1 (226-300)	**<0.001**
Relative uNGAL, µg/gCr	22.0 (9.5-52.3)	39.9 (20.2-80.5)	**0.01**
Relative uKIM-1, µg/gCr	1.35 (0.6-2.6)	2.02 (1.1-4.2)	**0.009**
Relative uIL-18, ng/gCr	11.5 (6-31)	16.7 (11-29)	0.52

Data are shown as median(Q1-Q3). Statistically significant P values are in bold.

Abbreviatures: NGAL, neutrophil gelatin associated lipocalin; KIM-1, kidney injury molecule 1; IL-18, interleukine-18.

Table S3: Cox regression analysis: Prognostic values for the outcome of readmission for recurrent heart failure

	Multivariable 4-month			Multivariable 12-month		
	HR	95%CI	*P*	HR	95%CI	*P*
LVEF <50%	0.541	0.259-1.132	0.10	0.645	0.366-1.137	0.13
AKI	1.121	0.524-2.402	0.77	1.006	0.532-1.903	0.99
Anemia	1.961	0.944-4.073	0.07	1.465	0.769-2.790	0.25
Urea	0.898	0.616-1.309	0.56	1.005	0.741-1.362	0.98
Albumin	0.775	0.523-1.149	0.21	0.960	0.694-1.326	0.80
NTproBNP	1.116	0.738-1.688	0.60	1.300	0.922-1.833	0.13
Dis sNGAL	1.561	0.986-2.472	0.06	1.511	1.060-2.155	**0.02**
Relative uNGAL	1.061	0.733-1.536	0.75	1.004	0.751-1.343	0.98
Relative uKIM-1	0.745	0.528-1.053	0.095	0.843	0.622-1.142	0.27

Data from n=187 patients were analyzed for all variables. Marked in bold are variables showing significance (P<0.05). Quantitative variables were transformed into typified variables (ln X-mean/SD).

Abbreviatures: HR, hazard ratio; AKI, acute kidney injury; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal proBNP fragment; CysC, cystatin C; NGAL, neutrophil gelatin associated lipocalin; KIM-1, kidney injury molecule 1.

Table S4: Cox regression analysis: Prognostic values for the combined outcome of all-cause mortality and/or readmission due to heart failure recurrence.

	Multivariable 4-month			Multivariable 12-month		
	HR	95%CI	*P*	HR	95%CI	*P*
LVEF <50%	0.648	0.342-1.229	0.18	0.711	0.424-1.190	0.19
AKI	1.130	0.564-2.263	0.73	1.107	0.623-1.967	0.73
Anemia	1.645	0.841-3.218	0.15	1.284	0.705-2.338	0.41
Urea	0.956	0.683-1.338	0.79	1.066	0.813-1.399	0.64
Albumin	0.775	0.558-1.076	0.13	0.913	0.695-1.200	0.51
NTproBNP	1.333	0.917-1.937	0.13	1.438	1.054-1.960	**0.02**
Dis sNGAL	1.486	0.988-2.234	0.06	1.473	1.064-2.038	**0.02**
Relative uNGAL	0.996	0.717-1.383	0.98	0.987	0.759-1.283	0.92
Relative uKIM-1	0.980	0.713-1.347	0.90	0.972	0.748-1.263	0.83

Data from n=187 patients were analyzed for all variables. Marked in bold are variables showing significance (P<0.05). Quantitative variables were transformed into typified variables (ln X-mean/SD).

Abbreviatures: HR, hazard ratio; AKI, acute kidney injury; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal proBNP fragment; CysC, cystatin C; NGAL, neutrophil gelatin associated lipocalin; KIM-1, kidney injury molecule 1.

Table S5: Biomarker values and operating characteristics for the prediction of acute kidney injury

	Total	**no AKI**	**AKI+**	***P***	**AUC***
Urea, g/L	0.55 (0.4-0.7) [204]	0.49 (0.4-0.7) [146]	0.73 (0.6-0.9) [58]	**<0.001**	0.732
sCreatinine, mg/dL	1.1 (0.9-1.4) [204]	1.1 (0.8-1.3) [146]	1.3 (1-1.7) [58]	**<0.001**	0.696
Baseline sCreatinine, mg/dL	1.1 (0.8-1.3) [204]	1.1 (0.8-1.3) [146]	1.0 (0.9-1.3) [58]	0.92	0.532
Cystatin C, mg/L	1.45 (1.15-1-81) [204]	1.4 (0.6-2.5) [146]	1.7 (1.4-1.9) [58]	**<0.001**	0.676
Admission sNGAL, ng/mL	168.3 (117-227) [171]	153.2 (117-211) [125]	214.4 (162-263) [46]	**<0.001**	0.667
Discharge sNGAL, ng/mL	187.5 (141-259) [170]	179.0 (126-233) [125]	255.8 (185-305) [45]	**0.001**	0.659
uCreatinine, mg/mL	58.7 (44-92) [162]	62 (43-94) [114]	55.4 (46-75) [48]	0.11	0.440
Relative uNGAL, µg/gCr	23.3 (11-57) [161]	21.3 (10-53) [113]	35.4 (14-75) [48]	0.07	0.598
Relative uKIM-1, µg/gCr	1.56 (0.6-2.8) [162]	1.42 (0.63-2.60) [114]	1.75 (0.59-3.75) [48]	**0.006**	0.569
Relative uIL-18, ng/gCr	12.8 (6-32) [159]	13.0 (6-31) [111]	11.7 (6-24) [48]	0.46	0.469

Values are shown as median(Q1-Q3). The number of subjects analyzed for either variable is indicated between brackets [n]. Statistically significant P values are in bold.

*Area Under the Curve (AUC) values were calculated using data from patients with all variables analyzed (n=135).

Abbreviatures: AKI, acute kidney injury; NGAL, neutrophil gelatin associated lipocalin; KIM-1, kidney injury molecule 1; IL-18, interleukine-18.

Table S6: Correlations between renal function and tubule damage markers

	sNGALadm	sNGALdis	uNGALr	uKIM-1r	uIL18r	eGFR	Creatinine	Uric Acid	Urea	Cystatin C
sNGALadm	1.000	**.694****	**.182***	.123	-.101	**-.477****	**.464****	**.257****	**.407****	**.476****
sNGALdis	**.694****	1.000	**.238****	.082	-.050	**-.509****	**.485****	**.201****	**.410****	**.527****
uNGALr	**.182***	**.238****	1.000	**.251****	**.214****	**-.204****	.045	.021	.138	**.180***
uKIM-1r	.123	.082	**.251****	1.000	.031	-.052	.038	.054	**.186***	**.187***
uIL18r	**-.101**	-.050	**.214****	.031	1.000	.008	-.088	.002	.019	**-.171***
eGFR	**-.477****	**-.509****	**-.204****	-.052	.008	1.000	**-.914****	**-.441****	**-.714****	**-.748****
Creatinine	**.464****	**.485****	.045	.038	-.088	**-.914****	1.000	**.445****	**.688****	**.750****
Uric Acid	**.257****	**.201****	.021	.054	.002	**-.441****	**.445****	1.000	**.408****	**.338****
Urea	**.407****	**.410****	.138	**.186***	.019	**-.714****	**.688****	**.408****	1.000	**.581****
Cystatin C	**.476****	**.527****	**.180***	**.187***	**-.171***	**-.748****	**.750****	**.338****	**.581****	1.000

Spearman's rho is shown for each correlation. Bold numbers indicate 2-tailed significances * <0.005, **<0.001. NGAL was determined in serum at admission and discharge. Urinary biomarkers were determined at discharge. All renal function parameters are at admission. GFR was estimated using the MDRD equation, and similar results were obtained using alternative formulas.

Abbreviatures: eGFR, estimated glomerular filtration rate; NGAL, neutrophil gelatin associated lipocalin; KIM-1, kidney injury molecule 1; IL-18, interleukine-18.

Table S7: Biomarkers levels and glomerular filtration rate

	eGFR > 60	eGFR < 60	*P*
Admission sNGAL, ng/mL	135.3 (93-184)	208.9 (163-262)	**<0.001**
Discharge sNGAL, ng/mL	149.4 (103-221)	232.8 (182.9-303.4)	**<0.001**
Relative uNGAL, µg/gCr	21.3 (9.5-55.3)	35.2 (14-65)	0.10
Relative uKIM-1, µg/gCr	1.19 (0.63-2.61)	1.77 (0.63-3.04)	0.06
Relative uIL-18, ng/gCr	12.9 (6.1-26.1)	12.4 (6.5-32.4)	**0.03**

Data are shown as median (Q1-Q3). GFR was estimated using the MDRD formula. Similar results were obtained using alternative formulas. Statistically significant P values are in bold.