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Prognostic value of neutrophil gelatinase-associated lipocalin in acute heart failure ☆

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ABSTRACT

Background: The identification of patients at risk for worse outcome is still a challenge. We hypothesized that cystatin C, a marker of renal function, and neutrophil gelatinase-associated lipocalin (NGAL), a marker of acute renal injury, would have a role in the prognostic stratification of these patients.
Methods: We prospectively evaluated 121 patients admitted for acute HF. Serum NGAL and cystatin C levels were measured on the first morning after admission. The outcome measures used were the occurrence of death from all causes, and the combined endpoint defined as the first occurrence of either death or hospital admission. Patients were followed for up to 3 months.
Results: The variables associated with a higher occurrence of death in a univariate approach were older age and higher levels of BNP, cystatin C and NGAL, and those associated with the occurrence of the combined endpoint were older age, Diabetes *mellitus*, lower GFR, type 1 cardio-renal syndrome, BNP, cystatin C and NGAL. BNP and NGAL remained independent predictors of the occurrence of both all-cause death and the combined endpoint. NGAL levels in the 75th percentile (>167.5 ng/mL) were associated with a 2.7-fold increase in the risk of death and a 2.9-fold increase in the risk of the first occurrence of either death or hospitalization.
Conclusions: Serum NGAL, a marker of acute renal injury, is an independent predictor of worse short term prognosis in patients with acute HF. This suggests a role of renal damage, apart from renal function, in the prognosis of these patients.

1. Introduction

Acute heart failure (HF) is the most common cause of hospital admission in persons older than 65 years [1]. The prognosis of patients admitted for acute HF is dismal, with a mortality rate of 6,7% during hospitalization and 13,5% at 3 months [2,3]. The re-hospitalization rate remains very high, with 24% at 3 months and in the range of 30% to 50% during the first year [3,4]. The identification of patients at high risk of an adverse outcome is still a challenge to clinicians. A variety of predictors of ominous prognosis have been identified. Eleven to forty percent of the patients hospitalized for acute decompensated HF develop WRF during hospital stay [5] and WRF has been reported to be associated with higher in-hospital mortality, increased all-cause re-hospitalization rates and longer duration of hospital stay [6–9].

Cystatin C is a cysteine protease inhibitor synthesized by nucleated cells that is freely filtered in the glomerulus, completely reabsorbed in the convoluted proximal tubule, and is not secreted. Cystatin C levels are not affected by sex, age, race, or muscle mass. Previous reports suggested that cystatin C can have a role in prognosis stratification of acute HF patients [10–12].

Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein synthesized in the bone marrow during granulocyte maturation. Granulocytes, epithelial cells, renal tubular cells, and hepatocytes release NGAL during injury, and its levels are significantly elevated in epithelial damage [13–15]. Several reports have suggested that NGAL levels (both urinary and serum) are elevated in patients with acute kidney injury and type 1 cardio-renal syndrome and this rise in NGAL levels is known to precede the plasma creatinine increase [16–20]. We have previously reported that a single NGAL measurement independently predicts the development of type 1 cardio-renal syndrome in acutely decompensated HF patients, suggesting that it might be a useful biomarker in the early recognition of these patients [21].

Abbreviations: HF, heart failure; WRF, worsening renal function; NGAL, neutrophil gelatinase-associated lipocalin; GFR, glomerular filtration rate.

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Table 1
Baseline characteristics of patients as a function of death, and variables associated with all-cause death.

	Total n = 120	Death		p	HR (95% CI)	p value
		Yes (n = 27)	No (n = 93)			
Age (years), media (SD); per year	75.2 (±12.6)	82.6 (±10.3)	73.0 (±12.4)	<0.001	1.08 (1.04–1.12)	<0.001
Male sex, n (%)	61 (50.8)	12 (44.4)	49 (52.7)	0.59	0.79 (0.37–1.69)	0.55
Diabetes *mellitus*, n (%)	30 (25.0)	6 (22.2)	24 (25.8)	0.90	0.87 (0.35–2.16)	0.76
LVEF (%), median (IQR); per 1%	35 (25–45)	35 (29–46)	35 (24–45)	0.59	1.01 (0.97–1.04)	0.70
LVEF<45% (vs. HFPEF), n (%)	80 (67.2)	18 (69.2)	62 (66.7)	0.99	1.16 (0.51–2.68)	0.72
NYHA IV (vs. III), n (%)	80 (66.7)	21 (77.8)	59 (63.4)	0.25	1.93 (0.78–4.79)	0.16
Systolic blood pressure (mm Hg), media (SD); per mm Hg	123 (±28)	114 (±21)	125 (±29)	0.06	0.99 (0.97–1.00)	0.07
Heart rate (bpm), media (SD); per bpm	85 (±20)	85 (±17)	85 (±21)	0.82	1.00 (0.98–1.02)	0.86
Diuretic at admission, n (%)	106 (88.3)	26 (96.3)	80 (86.0)	0.19	3.79 (0.51–27.94)	0.19
Diuretic dose at admission (mg/day), median (IQR); per mg/day	80 (60–100)	80 (60–100)	80 (60–100)	0.42	1.00 (0.99–1.02)	0.40
ACEi or ARB, n (%)	81 (67.5)	17 (63.0)	64 (68.8)	0.74	0.82 (0.38–1.80)	0.62
Beta-blocker, n (%)	61 (50.8)	12 (44.4)	49 (52.7)	0.59	0.76 (0.36–1.63)	0.48
GFR (mL/min per 1.73 m^2), median (IQR); per mL/min	40.0 (±16.5)	36.6 (±15.4)	41.3 (±16.7)	0.20	0.98 (0.96–1.01)	0.16
CRS1, n (%)	22 (18.3)	8 (29.6)	14 (15.1)	0.15	2.23 (0.98–5.09)	0.06
BNP (pg/mL), median (IQR); per 100 pg/mL	1594 (773.0–2702.0)	2496 (995.0–3785.0)	1368 (689.4–2285.5)	0.004	1.18 (1.08–1.30)	<0.001
Cystatin C (mg/L), media (SD); 75th percentile vs. others	1.70 (0.79)	2.00 (0.96)	1.59 (0.69)	0.02	1.76 (1.16–2.66)	0.008
NGAL (ng/mL), median (IQR); 75th percentile vs. others	95.0 (62.0–167.5)	98.0 (77.0–213.0)	91.0 (60.0–147.0)	0.08	1.04 (1.02–1.06)	<0.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; bpm, beats per minute; CI, confidence interval; GFR, glomerular filtration rate; CRS1, type 1 cardio-renal syndrome; HR, hazard ratio; HFPEF, heart failure with preserved ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; NGAL, neutrophil gelatinase-associated lipocalin; NYHA, New York Heart Association; SD, standard deviation.

There is an increasing body of evidence supporting the prognostic impact of several markers of tubulo-interstitial damage, including NGAL, in various renal disorders [14,22–24]. In HF, contrariwise, the prognostic value of these markers has not been well established. In a recent study, both urinary kidney injury molecule-1 and N-acetyl-β-(D)-glucosaminidase, but not NGAL, showed to add prognostic information to glomerular filtration rate (GFR) in chronic HF patients [25], suggesting an important role for tubular damage in cardio-renal interaction in HF. Recently, higher serum NGAL levels were reported to be associated with poorer 2-year survival in a chronic HF population [26].

We aimed to evaluate the short term prognostic significance of biomarkers of renal function and injury in acute HF patients.

2. Materials and methods

2.1. Study sample

We prospectively studied 121 patients admitted to our Internal Medicine Department between May and November 2009 with the diagnosis of acute HF. Patients were eligible whether acute HF was *de novo* or an exacerbation of chronic HF symptoms with an increase in at least one New York Heart Association class. HF diagnosis was based on the European Society of Cardiology criteria. Patients with an acute coronary syndrome and patients on chronic renal function replacement therapy were excluded.

The study protocol conformed the Declaration of Helsinki, local ethics committee approved the study and patients gave informed consent.

2.2. Study design

Fasting venous blood samples were collected between 8:00 and 9:00a.m. on the first morning after admission. NGAL and cystatin C levels were measured on the first morning after admission. Specimens were centrifuged for 10 min at 3000 ×*g* within 2 h after laboratory arrival. Analytical parameters were measured at the Hospital de São João Clinical Pathology Department. NGAL measurement was made with the Triage NGAL test system using EDTA-anticoagulated whole blood. This test system is a rapid, point-of-care fluorescence detection immunoassay using the Triage meter (Biosite, Quilaban, Lisboa, Portugal). Several drops of blood are added to the sample port in the device. After addition of the sample, the blood cells are separated from the plasma using a filter contained in the test device. The results are displayed in approximately 15 min. The manufacturer provided the calibration curve. For each 24 patient samples in which NGAL was determined, one control was performed. The lowest detectable concentration is 60 ng/mL, and the test has been demonstrated to be linear from 60 to 1300 ng/mL NGAL (which is considered the measurable range). We found a within-run precision of 19.3% for a sample with an average 132 ng/mL. Serum cystatin C was assayed using a particle-enhanced immunonephelometric assay (N Latex Cystatin C,

Table 2
Baseline characteristics of patients as a function of death or hospitalization, and variables associated with death or hospitalization.

	Death or hospitalization		p	HR (95% CI)	p value
	Yes (n = 53)	No (n = 67)			
Age (years), media (SD); per year	77.8 (±12.0)	73.1 (±12.8)	0.04	1.03 (1.00–1.05)	0.04
Male sex, n (%)	27 (50.9)	34 (50.7)	1.00	1.05 (0.61–1.80)	0.86
Diabetes *mellitus*, n (%)	18 (34)	12 (17.9)	0.07	2.00 (1.13–3.54)	0.02
LVEF (%), median (IQR); per 1%	38 (27–45)	35 (23–45)	0.42	1.01 (0.98–1.03)	0.54
LVEF<45% (vs. HFPEF), n (%)	35 (67.3)	45 (67.2)	1.00	1.03 (0.58–1.83)	0.93
NYHA IV (vs. III), n (%)	38 (71.7)	42 (62.7)	0.40	1.43 (0.79–2.60)	0.24
Systolic blood pressure (mm Hg), media (SD); per mm Hg	121 (±26)	124 (±29)	0.51	1.00 (0.98–1.01)	0.84
Heart rate (bpm), media (SD); per bpm	83 (±18)	87 (±22)	0.27	0.99 (0.98–1.01)	0.29
Diuretic at admission, n (%)	50 (94.3)	56 (83.6)	0.09	2.75 (0.86–8.83)	0.09
Diuretic dose at admission (mg/day), median (IQR); per mg/day	80 (60–100)	80 (60–100)	0.40	1.00 (1.00–1.01)	0.29
ACEi or ARB, n (%)	35 (66.0)	46 (68.7)	0.91	0.95 (0.54–1.68)	0.86
Beta-blocker, n (%)	23 (43.4)	38 (56.7)	0.21	0.68 (0.39–1.16)	0.16
GFR (mL/min per 1.73 m^2), median (IQR); per mL/min	35.7 (±15.4)	43.8 (±16.6)	0.008	0.98 (0.96–0.99)	0.006
CRS1, n (%)	14 (26.4)	8 (11.9)	0.07	1.99 (1.08–3.67)	0.03
BNP (pg/mL), median (IQR); per 100 pg/mL	1797 (916.5–3233.0)	1277 (626.0–2268.0)	0.04	1.12 (1.04–1.21)	0.005
Cystatin C (mg/L), media (SD); 75th percentile vs. others	1.91 (0.84)	1.50 (0.66)	0.004	1.66 (1.22–2.26)	0.001
NGAL (ng/mL), median (IQR); 75th percentile vs. others	102.0 (76.0–202.0)	84.0 (60.0–139.0)	0.02	1.04 (1.02–1.05)	<0.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blocker; BNP, B-type natriuretic peptide; bpm, beats per minute; CI, confidence interval; GFR, glomerular filtration rate; CRS1, type 1 cardio-renal syndrome; HR, hazard ratio; HFPEF, heart failure with preserved ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; NGAL, neutrophil gelatinase-associated lipocalin; NYHA, New York Heart Association; SD, standard deviation.

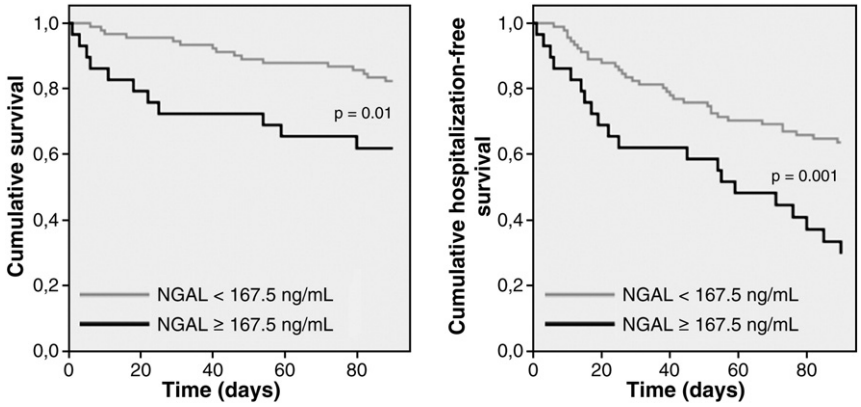

Fig. 1. Kaplan–Meier estimates of survival and hospitalization-free survival according to serum NGAL levels. Patients in the highest NGAL quartile have a significantly worse short term prognosis than the ones in the other quartiles.

Siemens, Lisboa, Portugal) on a BN II laser nephelometer. The lower limit of detection is 0.05 mg/L, and the within-run and the run-to-run variation was <5%. Plasma B-type natriuretic peptide was measured using an Architect i2000 automated analyzer (Abbott, Lisboa, Portugal). Serum creatinine, urea and albumin were measured using conventional methods with an Olympus AU5400 automated clinical chemistry analyzer. (Beckman-Coulter, Izasa, Porto, Portugal). Blood counts were obtained using an automated blood counter (Sysmex XE-5000; Emílio de Azevedo Campos, Porto, Portugal). GFR was estimated according to the Modification of Diet in Renal Disease (MDRD) formula: $GFR = 170 \times [PCr]^{-0.999} \times [Age]^{-0.176} \times [PU]^{-0.170} \times [Albumin]^{+0.318} \times [0.762 \text{ if female}] \times [1.180 \text{ if black}]$ [27–29]. All patients performed an echocardiogram and the left ventricular ejection fraction was determined using the modified Simpson method. Left ventricular systolic function was considered preserved if the left ventricular ejection fraction was ≥45%. Patients received standard treatment according to the attending physicians. Physicians were blinded to NGAL and cystatin C levels. Type 1 cardio-renal syndrome was defined as an increase in the creatinine level of at least 0.3 mg/dL or 50% of basal creatinine during hospitalization.

The outcome measures used to determine the prognostic importance of serum NGAL and cystatin C were the occurrence of death from all causes, and the combined endpoint defined as the first occurrence of either death or hospital admission. Information about the outcomes was obtained searching on our hospital records and by telephone contact with the patients. Patients were followed for up to 3 months after the first day of hospitalization. One patient was lost to follow-up.

2.3. Statistical analysis

Numerical variables are presented as mean (standard deviation) if normally distributed or median (interquartile range) if non-normally distributed. Categorical variables are presented as count (percent). Patients who developed the study outcomes and those who did not were compared: the χ^2 test was used to compare categorical variables, a two independent-sample *t* test was used to compare normally distributed variables, and the Mann–Whitney *U* test was used for skewed variables. We used Kaplan–Meier curves to display survival and hospitalization-free survival depending on serum NGAL and cystatin C levels. The study sample was categorized according to the 75th percentile of NGAL and cystatin C: 167.5 ng/mL and 1.98 mg/L, respectively. BNP was analyzed per 100 pg/mL increases. A Cox regression analysis was used to assess which variables predicted both the isolated and the combined endpoints. A multivariate model was built based on the variables associated with the outcome in the univariate approach. All of the analyses were conducted using SPSS 18.0 (SPSS, Inc., Chicago, IL). $p<0.05$ was considered to be statistically significant.

3. Results

Clinical characteristics of the study patients are presented in Table 1. A comparison between those who developed the study outcomes and those who did not are presented in Tables 1 and 2. At 90 days 27 (22.5%) patients died and 53 (44.2%) met the combined endpoint of death or hospital admission. Patients who died were older and presented higher levels of plasma BNP and serum cystatin C at hospital admission. There was a trend for lower systolic blood pressure measurements and higher levels of serum NGAL in this group. Patients who met the combined endpoint of death or hospitalization were also older, had lower GFRs and higher levels of BNP, cystatin C and NGAL. There was a propensity for having a prior diagnosis of Diabetes *mellitus*, for being under diuretics at the time of hospital admission and for developing type 1 cardio-renal syndrome during hospitalization.

The variables associated with a higher occurrence of death in the univariate analysis were older age and higher levels of BNP, cystatin C and NGAL. Patients developing type 1 cardio-renal syndrome presented a higher risk of death, nevertheless it did not reach statistical significance. Similarly, the variables associated with the occurrence of the combined endpoint of death or hospitalization were older age, the presence of Diabetes *mellitus*, lower GFR, type 1 cardio-renal syndrome, BNP, cystatin C and NGAL.

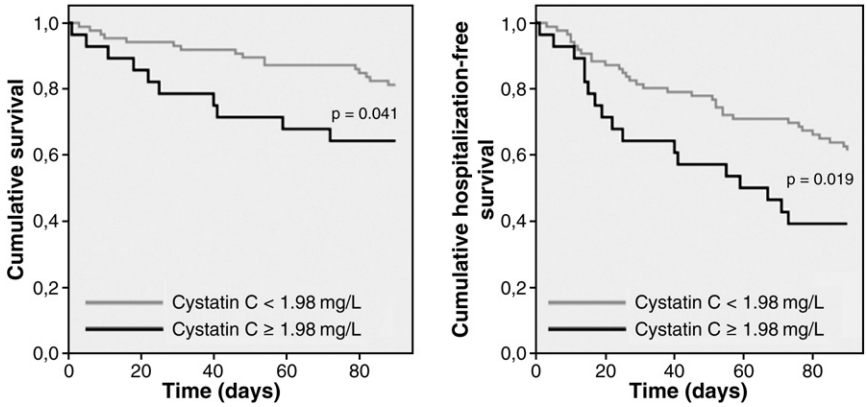

Fig. 2. Kaplan–Meier estimates of survival and hospitalization-free survival according to serum cystatin C levels. Patients in the highest cystatin C quartile have a significantly worse short term prognosis than the ones in the other quartiles.

Table 3
Multivariate model for prediction of all-cause death.

	Death	
	HR (95% CI)	p value
Age, per year	1.065 (1.025–1.107)	0.001
BNP, per 100 pg/mL	1.017 (1.006–1.027)	0.002
NGAL, 75th percentile vs. others	2.696 (1.203–6.041)	0.016
CRS1		0.339
Cystatin C, 75th percentile vs. others		0.771

Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; CRS1, type 1 cardio-renal syndrome; HR, hazard ratio; NGAL, neutrophil gelatinase-associated lipocalin.

Table 4
Multivariate model for prediction of death or hospitalization.

	Death or hospitalization	
	HR (95% CI)	p value
BNP, per 100 pg/mL	1.014 (1.005–1.022)	0.002
NGAL, 75th percentile vs. others	2.860 (1.593–5.136)	<0.001
Age, per year		0.153
Diabetes *mellitus*		0.061
GFR, per mL/min		0.360
CRS1		0.257
Cystatin C, 75th percentile vs. others		0.621

Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; GFR, glomerular filtration rate; CRS1, type 1 cardio-renal syndrome; HR, hazard ratio; NGAL, neutrophil gelatinase-associated lipocalin.

Kaplan–Meier curves show that patients with baseline serum NGAL above the 75th percentile (167.5 ng/mL) had a significantly higher 3-month mortality and higher occurrence of the combined endpoint of death or hospitalization (Fig. 1) than the patients with lower NGAL levels. Similarly, patients with baseline serum cystatin C above the 75th percentile (1.98 mg/L) also performed worse within the 3-month follow-up period, weather considering the isolated or the combined endpoint (Fig. 2).

Tables 3 and 4 show the multivariate models built. Older age and higher levels of BNP and NGAL were independently associated with a higher occurrence of death. Higher levels of BNP and NGAL were also independent predictors of the occurrence of the combined outcome of death or hospitalization. NGAL levels in the 75th percentile (>167.5 ng/mL) were associated with a 2.7-fold increase in the 3-month risk of death and a 2.9-fold increase in the 3-month risk of the first occurrence of either death or hospitalization.

4. Discussion

In our study sample, serum NGAL was an independent predictor of worse short term prognosis, namely of the occurrence of death or the combined outcome of death or hospitalization, when measured at admission in patients hospitalized for acute HF. Serum NGAL levels above 167.5 ng/mL predicted an almost 3-fold increase in morbidity and mortality within 3 months after admission for acute HF. The interplay between heart and kidney in HF has gathered growing interest in recent years and has been subject of intense and increasing clinical investigation. The actual knowledge emphasizes the role of the damaged heart signaling the kidneys through hemodynamic factors [30]. However, it is recognized that this interaction is most probably bidirectional. Other factors of the damaged heart contributing to kidneys damage as well as factors from the damaged kidney acting in the heart are currently under investigation.

NGAL is a biomarker reflecting damage to renal tubular cells, whose urinary and serum levels have been shown to be highly increased in patients with acute and chronic renal injury in different stages and settings [14,16–20,22–24,31,32]. NGAL levels rise in urine and serum as early as from 2 h onwards after an acute insult to the kidneys [16–20], and they can help predicting early type 1 cardio-renal syndrome development in patients admitted with worsening HF [21].

In the present report of 121 patients with acute HF, NGAL strongly predicted higher short term morbidity and mortality. This predictive power was independent of other variables also associated with the outcome, namely indexes of baseline renal function. In several previous reports the prognostic value of WRF in acute HF has been consistently shown and this has been true whether renal function is evaluated based on plasma creatinine, GFR or cystatin C [[],[]]. In our population, although renal function, as measured by MDRD and cystatin C, showed prognostic value in an univariate approach, in the multivariate model built, only NGAL independently predicted worse outcome, suggesting a role of renal injury, besides that of renal function and independent of it, upon the beginning of acute HF episodes.

Moreover, as far as we could understand from literature review, these are the first data on the prognostic impact of NGAL levels in an acute HF setting, thus broadening its predictive properties beyond the spectrum of renal disease.

Limitations of our study include the relatively small sample size and its single-centered nature. The observational design precluded the evaluation of the possible prognostic implications of clinical management changes based on admission NGAL levels. This was not, however, an objective of the study. Our results do not clarify if the increase in NGAL results from acute kidney injury or if it is associated with tubulo-interstitial chronic injury, as suggested by the observed increase in urinary NGAL in chronic HF with worse outcome [26]. Nevertheless, this study was able to test our hypothesis and to detect an independent association of increased NGAL levels with worse outcomes in acute HF patients, suggesting a role of renal damage, apart from renal function, in the prognosis of patients with a failing heart. Algorithms for risk stratification of acute HF patients would probably be enriched if renal injury measurements, namely NGAL, were included.

5. Conclusions

High serum NGAL independently predicts worse short term prognosis in patients with acute HF, with levels in the highest quartile, above 167.5 ng/mL, forecasting an almost 3-fold increase in morbidity and mortality within 3 months after admission. These results suggest that, in acute HF, renal injury, beyond renal function, has a relevant role in the interaction between heart and kidney.

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The authors of this manuscript have certified that they comply with the principles of ethical publishing in the International Journal of Cardiology.

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