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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.