International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Influence of renal dysfunction phenotype on mortality in decompensated heart failure with preserved and mid-range ejection fraction☆

Jesús Casado [a,*], Marta Sánchez [b], Vanesa Garcés [b], Luis Manzano [c], José Manuel Cerqueiro [d], Francisco Epelde [e], David García-Escrivá [f], José Pérez-Silvestre [f], José Luis Morales [g], Manuel Montero-Pérez-Barquero [h], on behalf of RICA Investigators Group

[a] Hospital Universitario de Getafe, Madrid, Spain
[b] Hospital Clinico Universitario "Lozano Blesa", IIS Aragon, Zaragoza, Spain
[c] Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid, Spain
[d] Hospital Universitario Lucus Augusti, Lugo, Spain
[e] Corporació Sanitària Parc Taulí, Barcelona, Spain
[f] Hospital General Universitario de Valencia, Valencia, Spain
[g] Hospital Universitario Arnau de Vilanova, Lleida, Spain
[h] IMIBIC/Hospital Universitario Reina Sofía, Universidad de Córdoba, Córdoba, Spain

ARTICLE INFO

Article history:
Received 7 October 2016
Accepted 10 May 2017
Available online xxxx

Keywords:
Renal dysfunction
NT-proBNP
Blood urea nitrogen to creatinine ratio
Heart failure with preserved ejection fraction
Heart failure with mid-range ejection fraction

ABSTRACT

Background: Natriuretic peptides or the blood urea nitrogen to creatinine ratio (BUN/creat) can identify high- vs low-risk renal impairment (RI) in patients with heart failure and reduced ejection fraction (HF-REF). However, the situation in HF patients with preserved ejection fraction (HF-PEF) and mid-range ejection fraction (HF-MREF) remains unclear.

Methods: We evaluated patients from the Spanish National Registry of Heart Failure (RICA) that were admitted to Internal Medicine units with acute decompensated HF. Median admission values were used to define elevated NT-proBNP and BUN/creat.

Results: A total of 935 patients were evaluated, 743 with HF-PEF and 192 with HF-MREF). In patients with both NT-proBNP and BUN/creat below median admission values, RI was not associated with mortality (HR 1.15; 95% CI 0.7–1.87, $p = 0.581$ in HF-PEF and HR 1.27; 95% CI 0.58–2.81, $p = 0.548$ in HF-MREF). However, in patients with both elevated NT-proBNP and BUN/creat, those with RI had worse survival than those without RI (HR 2.01, 95% CI 1.33–3.06, $p < 0.001$ in HF-PEF and HR 2.79, 95% CI 1.37–5.67, $p = 0.005$ in HF-MREF). In HF-PEF even patients with RI with only 1 of the 2 parameters elevated, had a substantially higher risk of death compared to patients without RI (HR 1.53; 95% CI 1.04 to 2.26; $p = 0.031$).

Conclusions: In this clinical cohort of acute decompensated HF-PEF and HF-MREF patients, the combined use of NT-proBNP and BUN/creat stratifies patients with RI into groups with significantly different prognoses.

1. Introduction

Renal dysfunction is highly prevalent among patients with acute and chronic heart failure (HF). Defined as baseline reduction in glomerular filtration, or a worsening of renal function over time, renal impairment (RI) is associated with increased mortality risk in patients with HF [1,2].

The relationship between cardiac disorders and RI is heterogeneous and not fully understood. Cardiorenal syndrome has been previously defined as the simultaneous dysfunction of both the heart and the kidney, and five distinct subtypes have been identified, depending on whether heart or kidney was the initial organ of insult [3]. However, limited data are available to support the distinction between cardiorenal syndrome subtypes based on pathophysiology and prognosis.

Worsening renal function that occurs as the result of initiation of renin-angiotensin-aldosterone system antagonism, titration of

☆ All the authors listed above takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Internal Medicine Service, Hospital Universitario de Getafe, Crta de Toledo Km. 12,500, Getafe, Spain.
E-mail address: jmanuel.casado@salud.madrid.org (J. Casado).

http://dx.doi.org/10.1016/j.ijcard.2017.05.048
0167-5273/

vasodilators, or successful decongestion appears to have limited prognostic value, suggesting that not all forms of RI are equivalent [4–7]. It seems then that the mechanisms underlying RI are critically important in determining the associated prognosis. Although the mechanistic basis for heart-failure-induced renal dysfunction has yet to be established, a prevailing theory is that excessive neurohormonal activation is an important mediator [3,8,9]. Urea plays a fundamental and direct role in fluid and sodium homeostasis [10,11]. As a result, during times of fluid and sodium avidity, such as intravascular volume depletion or HF, the rate of urea excretion is reduced out of proportion to the reduction in glomerular filtration, ultimately leading to an elevated BUN to creatinine ratio (BUN/creat) [12]. As this reabsorption process is directly or indirectly regulated by neurohormonal activity, BUN/creat has been proposed as a metric of neurohormonal activity [13]. Moreover, the neurohormonal connection between cardiac and renal impairment is not only via the renin-angiotensin-aldosterone system, but also via its antagonists like natriuretic peptides [14]. In line with this pathophysiological background, natriuretic peptide levels and BUN/creat may help to identify this neurohormonal activation, reflecting HF-induced renal dysfunction instead of intrinsic renal parenchymal disease. Previous studies demonstrate that the majority of mortality risk associated with RI is restricted to patients with elevation of either of these markers and that their combination produces even more striking results [15–18]. Unfortunately those studies focused on patients with reduced ejection fraction (HF-REF), and there is no data from individuals with preserved ejection fraction (HF-PEF) and mid-range ejection fraction (HF-MREF).

Accordingly, the primary aim of this study was to test hypothesis that the combination of amino-terminal pro-brain natriuretic peptide (NT-proBNP) and BUN/creat can identify high- vs low- mortality risk forms of RI in patients admitted for acute decompensated HF-PEF and HF-MREF.

2. Methods

2.1. Patients

Patient data were collected from the Spanish National Registry of Heart Failure (RICA), supported by the Spanish Working Group of Heart Failure of the Spanish Society of Internal Medicine. RICA is a multicenter, prospective, cohort study, the characteristics of which have been described elsewhere [19,20]. This registry includes data from 52 Spanish hospitals. The study complied with the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the "Hospital Universitario Reina Sofía", Córdoba, Spain. All patients consecutively admitted to Internal Medicine units with acute HF and seen by physicians participating in the registry were included in the study. In addition to giving their written informed consent, patients had to meet the following criteria: admission for HF, presenting with either a first episode of HF or decompensation of previously documented chronic HF. Exclusion criteria were HF due to pulmonary hypertension, unwillingness to participate in the study or death during the index admission. Follow-up consisted of two visits scheduled at 3 months and one year after discharge from the index admission.

For the purposes of this study, only patients with an ejection fraction higher than 50% or 40–49% and availability of admission NT-proBNP and BUN/creat levels were included in the analysis. This ejection fraction has been used previously to define HF-PEF and HF-MREF [21–23]. The primary endpoint was death from all causes in the first year after index admission.

2.2. Study variables

The registry included sociodemographic data, previous medical history, comorbidity (Charlson index) [24], baseline functional status for activities of daily living (Barthel index) [25], clinical data, laboratory evaluation, complications during hospitalisation, and prescriptions at discharge. HF severity was determined according to functional class [New York Heart Association (NYHA) class], 2D echocardiography, chest X-ray and ECG. Basic biochemical variables were obtained at the time of hospital admission. RI was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. Anaemia was defined using the World Health Organisation criteria: haemoglobin <12 g/dL in women and <13 g/dL in men.

The equation used for estimated renal function was the CKD-EPI equation: $141 \times \min(\text{serum creatinine}/\kappa, 1)^{\alpha} \times \max(\text{serum creatinine}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}}$ ($\times 1.018$ if female) ($\times 1.159$ if black), where "κ" is 0.7 for female and 0.9 for male, "α" is −0.329 for female and −0.411 for male, "min" is minimum serum creatinine/κ or 1 and "max" is maximum serum creatinine/κ or 1.

2.3. Statistical analysis

A descriptive analysis of the sample was conducted. Continuous variables were tested for a normal distribution with the Kolmogorov-Smirnov method. Normally distributed variables are presented as mean ± standard deviation and non-normally distributed variables as median with interquartile range. Categorical variables are expressed as percentages. Differences in baseline characteristics were compared with the use of Chi-squared tests for categorical variables and analysis of variance (ANOVA) and non-parametric tests of differences in median for quantitative variables.

For NT-proBNP analyses, patients were dichotomised to above or below median NT-proBNP levels [15]. For BUN/creat analyses, patients were dichotomised to above or below median BUN/creat levels [26]. For analyses of renal function, patients were dichotomised to eGFR above or below 60 mL/min/1.73 m^2, a cut-off value based on the standards of the National Kidney Foundation [17,18,27]. The primary analysis focused on determining the risk for all-cause mortality in the various groups, and patients without RI (eGFR ≥ 60 mL/min/1.73 m^2) were used as the reference. The data are described in terms of 4 groups: 1) eGFR ≥60 mL/min/1.73 m^2; 2) eGFR <60 mL/min/1.73 m^2 with a NT-proBNP *and* BUN/creat below the median values; 3) eGFR <60 mL/min/1.73 m^2 with a NT-proBNP *or* BUN/creat above the median values; and 4) eGFR <60 mL/min/1.73 m^2 with a NT-proBNP *and* BUN/creat above the median values [18]. The *p*-value for interactions between those sub-groups was <0.001.

Spearman correlation coefficients were used to examine statistical dependence between 2 variables. Univariate and multivariate analyses of baseline variables was used to identify independent predictors of all-cause one-year mortality and Cox proportional hazards models were performed for this purpose. Multivariate analyses were performed with the forward stepwise method, including all candidate variables with *p* values <0.05 in the univariate analyses. Survival curves were computed with the Kaplan-Meier curves, and differences between the curves were evaluated with the log-rank statistic.

Tests were two-tailed and *p*-values <0.05 were considered as statistically significant. All statistical analyses were performed using SPSS 20.0 statistical software packages (SPSS, Inc., Chicago, Illinois).

3. Results

Overall, 935 patients were included in the analysis, 743 patients admitted for acute HF-PEF and 192 patients admitted for acute HF-MREF. The median admission serum NT-proBNP concentration was 2696 pg/mL (1257–6163) and 3992 pg/mL (1589–8130) for HF-PEF and HF-MREF respectively. The median admission eGFR was 51 mL/min/1.73 m^2 (34.9–67.1) and 51.8 mL/min/1.73 m^2 (34.6–69.4) for HF-PEF and HF-MREF respectively. The median admission value of BUN/creat ratio was 24.1 (19–30.3) and 22.8 (17.6–28.4) for HF-PEF and HF-MREF respectively. A total of 493 (66.35%) HF-PEF patients and 121 (63.02%) HF-MREF patients had RI defined by eGFR <60 mL/min/1.72 m^2. Subjects with RI had higher admission median NT-proBNP concentrations than those without RI (3205 pg/mL vs 2088 pg/mL; $p < 0.001$ and 4813 pg/mL vs 2.517 pg/mL; $p < 0.001$ for HF-PEF and HF-MREF respectively). In the group of HF-PEF patients with RI, 124 (25.15%) patients had both a BUN/creat and NT-proBNP below the median, 235 (47.66%) had 1 of the 2 parameters elevated, and 134 (27.18%) had both parameters elevated. In the group of HF-MREF patients with RI, 46 (38.1%) patients had both a BUN/creat and NT-proBNP below the median, 39 (32.23%) had 1 of the 2 parameters elevated, and 36 (29.75%) had both parameters elevated. Baseline parameters of HF-PEF and HF-MREF patients with combinations of eGFR, NT-proBNP and BUN/creat can be found in Tables 1 and 2.

In HF-PEF patients BUN/creat demonstrated only a weak correlation with NT-proBNP ($r = 0.089$; $p = 0.015$). The correlation between eGFR and both BUN/creat ($r = 0.095$; $p = 0.010$) and NT-proBNP ($r = -0.305$; $p < 0.001$) was also weak. Correlations in HF-MREF were similar: $r = 0.206$, $p = 0.004$ between BUN/creat and NT-proBNP; $r = 0.067$, $p = 0.035$ between eGFR and BUN/creat; and $r = -0.350$, $p < 0.001$ between eGFR and NT-proBNP.

Overall, 186 (25%) HF-PEF patients and 47 (24.5%) HF-MREF patients died in the first year of follow-up after the index admission. In multivariate analyses, patients with RI but normal NT-proBNP and BUN/creat had a non-significant trend toward increased mortality, both in HF-PEF and HF-MREF patients (HR 1.15; 95% CI 0.7 to 1.87; $p = 0.581$ in HF-PEF and HR 1.27; 95% CI 0.58 to 2.81; $p = 0.548$ in HF-MREF). However, patients with HF-PEF and RI with only 1 of the 2 parameters elevated, and especially those with both elevated NT-proBNP and

Please cite this article as: J. Casado, et al., Influence of renal dysfunction phenotype on mortality in decompensated heart failure with preserved and mid-range ejection fraction, Int J Cardiol (2017), http://dx.doi.org/10.1016/j.ijcard.2017.05.048