A Combined-Biomarker Approach to Clinical Phenotyping Renal Dysfunction in Heart Failure

JEFFREY M. TESTANI, MD, MTR,[1] KEVIN DAMMAN, MD, PhD,[2] MEREDITH A. BRISCO, MD, MSCE,[3] SUSAN CHEN, MD,[1] OLGA LAUR, BS,[1] ALEXANDER J. KULA, BS,[1] W.H. WILSON TANG, MD,[4] AND CHIRAG PARIKH, MD, PhD[1]

New Haven, Connecticut; Groningen, The Netherlands; Charleston, South Carolina; Cleveland, Ohio

ABSTRACT

Background: Differentiating heart failure (HF) induced renal dysfunction (RD) from intrinsic kidney disease is challenging. It has been demonstrated that biomarkers such as B-type natriuretic peptide (BNP) or the blood urea nitrogen to creatinine ratio (BUN/creat) can identify high- vs low-risk RD. Our objective was to determine if combining these biomarkers could further improve risk stratification and clinical phenotyping of patients with RD and HF.

Methods and Results: A total of 908 patients with a discharge diagnosis of HF were included. Median values were used to define elevated BNP (>1296 pg/mL) and BUN/creat (>17). In the group without RD, survival was similar regardless of BNP and BUN/creat (n = 430, adjusted P = .52). Similarly, in patients with both a low BNP and BUN/creat, RD was not associated with mortality (n = 250, adjusted hazard ratio [HR] = 1.0, 95% confidence interval [CI] 0.6−1.6, P = .99). However, in patients with both an elevated BNP and BUN/creat those with RD had a cardiorenal profile characterized by venous congestion, diuretic resistance, hypotension, hyponatremia, longer length of stay, greater inotrope use, and substantially worse survival compared with patients without RD (n = 249, adjusted HR = 1.8, 95% CI 1.2−2.7, P = .008, P interaction = .005).

Conclusions: In the setting of decompensated HF, the combined use of BNP and BUN/creat stratifies patients with RD into groups with significantly different clinical phenotypes and prognosis. (*J Cardiac Fail 2014;20:912−919*)

Key Words: Cardiorenal syndrome, BNP, blood urea nitrogen to creatinine ratio, decompensated heart failure.

Introduction

In the setting of heart failure (HF), renal dysfunction (RD) has consistently been identified as one of the most powerful prognostic indicators available.[1,2] However, as research in this area accumulates, it has become clear that not all forms of RD are equivalent. Notably, worsening renal function that occurs as the result of initiation of renin-angiotensin-aldosterone system antagonism, titration of vasodilators, or successful decongestion appears to have limited prognostic importance.[3−6] Similarly, it has previously been described that the risk associated with a low estimated glomerular filtration rate (eGFR) is particularly pronounced in patients with high natriuretic peptide levels and we have found that an elevated blood urea nitrogen to creatinine ratio (BUN/creat) can also identify higher risk forms of RD.[7−9] The global interpretation of these findings is that the mechanisms underlying RD are critically important in determining the associated prognosis.

Although elevated natriuretic peptide levels (identifying patients with venous congestion and activation of compensatory cardiorenal pathways) and elevated BUN/creat (signifying activation of sodium conserving pathways and renal neurohormonal activation) can each identify high-risk RD; factors such as diet, protein catabolism, age, and body habitus affect the levels of these markers independent

From the [1]Department of Internal Medicine and Program of Applied Translational Research, Yale University School of Medicine, New Haven, Connecticut; [2]University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [3]Department of Internal Medicine, Medical University of South Carolina, Charleston, South Carolina and [4]Section of Heart Failure and Cardiac Transplantation, Cleveland Clinic, Cleveland, Ohio.

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Reprint requests: Jeffrey M. Testani, MD, MTR, Yale University, 60 Temple Street, Suite 6C, New Haven, CT 06510. Tel.: (215) 459−3709; Fax: (203) 746−8373. E-mail: jeffrey.testani@yale.edu

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of the cardiorenal axis. As a result, the specificity of each marker is somewhat limited. However, it is possible that a combination of these markers could more precisely identify patients with true HF-induced RD by querying 2 relatively independent mechanisms for cardiorenal dysfunction. Therefore, we hypothesized that patients with acute decompensated HF and both an elevated B-type natriuretic peptide (BNP) and BUN/creat should have a particularly pronounced risk for mortality attributable to RD, in conjunction with a clinical phenotype typical of cardiorenal dysfunction. The primary objectives of this study were to: 1) validate the finding that natriuretic peptide levels can identify high- and low-risk RD,[7] 2) evaluate if patients with RD and elevated BNP and BUN/creat will have a higher prevalence of findings thought typical of HF-induced RD such as baseline venous congestion and diuretic nonresponsiveness, and 3) determine if combination of BNP and BUN/creat can identify high- and low-risk forms of RD.

Methods

We reviewed the charts of all patients with a primary discharge diagnosis (determined using International Classification of Disease codes) of congestive HF who had been admitted to noninterventional cardiology and internal medicine services at the Hospital of the University of Pennsylvania between 2004 and 2009. Inclusion required a BNP level of >100 pg/mL within 24 hours of admission and availability of admission BUN/creat levels. Patients with a length of stay ≤ 2 days (who likely underwent limited decongestion) and patients with length of stay > 14 days (who likely had either atypical degrees of congestion or non-HF problems driving the length of stay) were excluded from the cohort. Patients receiving renal replacement therapy were also excluded. In the event of multiple hospitalizations for a single patient, only the first admission meeting the inclusion criteria was retained (see Supplementary Fig. 1 for additional details on patient selection). The ultimate sample size of 908 represents a ''convenience sample'' because it was determined via the patient availability and inclusion/exclusion criteria.

The 4-variable Modified Diet and Renal Disease equation was used to calculate eGFR.[10] All-cause mortality was determined via the Social Security Death Index.[11] Loop diuretic doses were converted to furosemide equivalents with 1 mg bumetanide = 20 mg torsemide = 80 mg furosemide for oral diuretics, and 1 mg bumetanide = 20 mg torsemide = 40 mg furosemide for intravenous diuretics.[12,13] The relative diuretic efficiency in each patient was determined as the fluid output per mg of loop diuretic received (expressed as mL of net fluid output per 40 mg of furosemide equivalents). Forty milligrams of furosemide equivalents was chosen as a reference because this is a dose reported to produce near maximal rate of instantaneous natriuresis in a healthy volunteer naive to diuretics.[14] The initial assembly of the cohort was approved by the Institutional Review Board at the Hospital of the University of Pennsylvania and transfer of a version of this dataset stripped of patient identifiers was determined by the Yale University Institutional Review Board to not qualify as human subject research.

Statistical Analysis

The primary goal of this analysis was to describe the clinical profile and prognosis of RD in patients with low-low BNP-BUN/creat or high-high BNP and BUN/creat using patients without RD as the reference. As such, the primary analysis focused on describing the clinical profile of these patients and determining the risk for all-cause mortality in the various groups. To minimize errors from multiple comparisons, 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 BNP *and* BUN/creat below the median values; 3) eGFR <60 mL·min·1.73 m^2 with a BNP *or* BUN/creat above the median values; and 4) eGFR < 60 mL·min·1.73 m^2 with a BNP *and* BUN/creat above the median values. A secondary objective was to validate the findings of van Kimmenade et al regarding effect modification of BNP on the risk associated with RD.[7] The primary outcome of this analysis was the interaction between BNP dichotomized about the median and an eGFR ≥60 mL·min·1.73 m^2 with respect to all-cause mortality. Values reported are mean ± standard deviation, median (quartile 1 − quartile 4) and percentile. The Kruskal-Wallis test was used to compare continuous variables across multiple groups. For comparison of continuous parameters between 2 groups the Mann-Whitney U test or t-test or was used. The Pearson chi-square was used to evaluate associations between categorical variables. The Jonckheere-Terpstra test for ordered alternatives was used as the test of trend. Correlations reported are Spearman's r. Proportional hazards modeling was used to evaluate time-to-event associations with all-cause mortality. Candidate covariates entered in the model were baseline characteristics with univariate all-cause mortality associations $P \leq .2$. Models were built using backward elimination (likelihood ratio) where all covariates with a $P < .2$ were retained.[15] The proportional hazards assumption was examined using time dependent covariates. A post-hoc power calculation demonstrated that with an alpha of 0.05 and a power of 80% the subgroup analyzed with low BUN/creat and low BNP (n = 250) an effect size of ≥1.43 would be detectable. Statistical analysis was performed with IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY) and Stata 12.0 (Statacorp, College Station, Texas). A 2-sided P value of < .05 was considered statistically significant aside from tests of interaction where a $P < .1$ was considered significant.

Results

Overall, 908 patients were included in the analysis. Baseline and in-hospital characteristics of the overall cohort are presented in Supplementary Tables 1 and 2. The median admission serum BNP level was 1296 pg/mL (660−2387), the median eGFR was 57.9 mL·min·1.73 m^2 (39.5−75.9) and the median value of BUN/creat was 17.0 (13.3−22.2). The strength of correlation between BUN/creat and BNP was small (r = 0.13, $P < .001$), as was the correlation between eGFR and both BUN/creat (r = −0.18, $P < .001$) and BNP (r = −0.22, $P < .001$). These modest correlations translated into 27.5% of the population having both a BUN/creat and BNP below the median, 45.0% with 1 of the 2 parameters elevated, and 27.4% with both parameters elevated. Baseline and in-hospital parameters of patients with the various combinations of an eGFR <60, an elevated BNP, and/or an elevated BUN/creat can be found in Tables 1 and 2 and Supplementary Tables 1 and 2. The change in BUN/creat from admission to discharge was statistically significant but modest in magnitude (1.9 ± 6.4,