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The risk of death associated with proteinuria in heart failure is restricted to patients with an elevated blood urea nitrogen to creatinine ratio

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ABSTRACT

Background: Renal dysfunction (RD) is associated with reduced survival in HF; however, not all RD is mechanistically or prognostically equivalent. Notably, RD associated with "pre-renal" physiology, as identified by an elevated blood urea nitrogen to creatinine ratio (BUN/Cr), identifies a particularly high risk RD phenotype. Proteinuria, another domain of renal dysfunction, has also been associated with adverse events. Given that several different mechanisms can cause proteinuria, we sought to investigate whether the mechanism underlying proteinuria also affects survival in HF.

Methods and Results: Subjects in the Studies of Left Ventricular Dysfunction (SOLVD) trial with proteinuria assessed at baseline were studied ($n = 6439$). All survival models were adjusted for baseline characteristics and estimated glomerular filtration rate (eGFR). Proteinuria (trace or 1+) was present in 26% and associated with increased mortality (HR = 1.2; 95% CI, 1.1–1.3, $p = 0.006$). Proteinuria >1+ was less common (2.5%) but demonstrated a stronger relationship with mortality (HR = 1.9; 95% CI, 1.5–2.5, $p < 0.001$). In patients with BUN/Cr in the top tertile (≥17.3), any proteinuria (HR = 1.3; 95% CI, 1.1–1.5, $p = 0.008$) and >1+ proteinuria (HR = 2.3; 95% CI, 1.7–3.3, $p < 0.001$) both remained associated with mortality. However, in patients with BUN/Cr in the bottom tertile (≤13.3), any proteinuria (HR = 0.95; 95% CI, 0.77–1.2, $p = 0.63$, p interaction = 0.015) and >1+ proteinuria (HR = 1.3; 95% CI, 0.79–2.2, $p = 0.29$, p interaction = 0.036) were not associated with worsened survival.

Conclusion: Analogous to a reduced eGFR, the mechanism underlying proteinuria in HF may be important in determining the associated survival disadvantage.

1. Introduction

Renal dysfunction (RD) is highly prevalent in heart failure (HF) and identifies patients at high-risk for mortality and cardiovascular events [1,2]. HF can precipitate RD through a number of mechanisms including increased neurohormonal activation, venous congestion and reduced perfusion [3,4]. However, many of the same risk factors that lead to HF such as diabetes and hypertension can also lead to primary intrinsic RD. Importantly, not all RD is prognostically equivalent [5–7]. For example, the mortality risk attributable to a reduced estimated glomerular filtration rate (eGFR) is largely restricted to patients with an elevated blood urea nitrogen to creatinine ratio (BUN/Cr; serving as a surrogate for increased neurohormonal activation), whereas RD in the setting of a low BUN/Cr fails to negatively impact survival [8,9].

Proteinuria is an established risk factor for mortality in cardiovascular and kidney disease and more recently has been shown to predict adverse outcomes in chronic HF [10–15]. Notably, the survival disadvantage associated with proteinuria in HF is independent of eGFR, suggesting proteinuria may serve as a distinct metric of cardio-renal risk in these patients. Similar to a reduced eGFR, proteinuria can be caused by several different mechanisms, many of which involve renal parenchymal damage from diseases such as diabetes and hypertension [16]. However, a "functional" form of proteinuria secondary to factors such as increased neurohormonal activation and venous congestion is well described, providing a plausible pathophysiologic connection between HF and proteinuria [17–19]. It is unknown whether the etiology of proteinuria influences its association with mortality.

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Given that an elevated BUN/Cr provides a surrogate for neurohormonal activation and can differentiate prognostically distinct forms of RD defined by a reduced eGFR, we hypothesized that the mortality risk associated with proteinuria would be primarily restricted to patients with a neurohormonally activated "pre-renal" cause for proteinuria identified by an elevated BUN/Cr [8,9,20,21]. As such, the primary goal of this analysis was to determine if BUN/Cr modified the association between proteinuria and mortality.

2. Methods

The SOLVD prevention and treatment trials were placebo controlled trials investigating the effect of enalapril on patients with asymptomatic and symptomatic left ventricular dysfunction and comprise the SOLVD limited dataset [22,23]. Briefly, 4228 patients were enrolled in the prevention trial and 2569 in the treatment trial across 23 international centers for a total of 6797 patients. An ejection fraction ≤35% was required for inclusion in either trial. Patients who were not receiving heart failure medications and were without evidence of overt heart failure at the end of a 3-week run-in period were eligible for the prevention trial. Eligibility for inclusion in the treatment trial required both a HF diagnosis and medical treatment for the condition. Patients with a baseline creatinine level >2.5 mg/dL, severe or unstable coronary or valvular disease, suspected renal artery stenosis, or any other disease suspected to shorten survival and impede participation in the long-term trial were excluded. Previous use of an angiotensin-converting enzyme inhibitor was not a criterion for exclusion.

The Modified Diet and Renal Disease equation was used to estimate GFR as per our previous analyses with this dataset [6,8]. RD was defined as an eGFR < 60 mL/min/1.73 m^2 [24]. Proteinuria was assessed at baseline and 6 weeks via urine dipstick into four categories: none, trace or 1+ proteinuria, 2+ proteinuria, and 3 or 4+ proteinuria. BUN/Cr was also assessed at baseline. As the median BUN/Cr was in the normal range in the SOLVD cohort, BUN/Cr was dichotomized and comparisons were made between the top tertile (BUN/Cr >17.3) and bottom tertile (BUN/Cr <13.3) referred to as high and low BUN/Cr, respectively. Patients without baseline urine dipstick ($n = 277$) or BUN/Cr ($n = 81$) assessment were excluded from this analysis. This manuscript was prepared using the SOLVD Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the SOLVD investigators or NHLBI. This study was deemed exempt by the institutional review boards at Medical University of South Carolina and Yale University.

3. Statistical analysis

Values reported are mean ± standard deviation, median (25th–75th percentile) and percentage. The independent Student *t* test or the Wilcoxon rank-sum test was used to compare continuous variables. The Pearson χ^2 was used to evaluate associations between categorical variables. Spearman correlation coefficients were used to examine statistical dependence between 2 variables. The primary objective of this analysis was to determine whether BUN/Cr could identify prognostically different subtypes of proteinuria. As a result, the primary outcome was the interaction between BUN/Cr and proteinuria (both any proteinuria and greater than 1+ proteinuria) on survival. Cox proportional hazards modeling was used to evaluate time-to-event associations with all-cause mortality. Candidate covariates for the multivariable models were obtained by screening clinical characteristics for an association with proteinuria, BUN/Cr or mortality at $p \leq 0.2$. Using backward elimination (likelihood ratio), covariates were removed and those with a $p < 0.2$ were retained in the final model [25]. Stratum-specific hazard ratios (HR) were derived from the proportional hazards models of the individual strata (high vs. low BUN/Cr). The significance of the interactions was formally assessed using models incorporating the main effect of proteinuria, the main effect of high vs. low BUN/Cr, and the interaction between these variables. Adjusted survival curves for all-cause mortality were plotted to examine the effect of both any proteinuria and greater than 1+ proteinuria in patients with low BUN/Cr and in patients with high BUN/Cr. Survival curves for death from any cause were also plotted for the four combinations of groups between higher and lower BUN/Cr combined with the presence or absence of proteinuria. Statistical analysis was performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY). A two-sided *p*-value of <0.05 was considered statistically significant with the exception of tests of interaction where significance was defined as $p < 0.10$.

4. Results

In total, 6439 patients were included in the analysis. Proteinuria was present in 25.8% of the population ($n = 1662$) of whom 155 patients had greater than 1+ proteinuria (2.5% of total population). Baseline characteristics of the population grouped by presence or absence of any baseline proteinuria are presented in Table 1. As expected, patients with proteinuria were more likely to have concomitant diabetes and hypertension; however, 75.4% of patients with proteinuria were without concomitant diabetes and 56.7% of patients with proteinuria were normotensive. There was no difference in etiology of heart failure, NYHA class or medication use among patients with or without proteinuria (Table 1). Markers of increased disease severity including tachycardia, hyponatremia and increased BUN were more common in patients with proteinuria (Table 1). Although RD was relatively more common in patients with vs. without proteinuria (OR = 1.49; 95% CI, 1.30–1.62, $p < 0.001$), a low eGFR was not requisite as 51.6% of patients with proteinuria did not have an eGFR <60 mL/min/1.73 m^2.

The mean baseline BUN/Cr of the population was in the normal range at 15.9 ± 5.18. Baseline BUN/Cr was weakly correlated with baseline eGFR ($r = 0.22$, $p < 0.001$) and baseline serum creatinine ($r = -0.13$, $p < 0.001$) yet demonstrated no correlation with baseline proteinuria ($r = 0.01$, $p = 0.70$). Baseline characteristics of patients with BUN/Cr in the top tertile (≥17.3, high) compared to BUN/Cr in the bottom tertile (≤13.3, low) are shown in Table 2. Patients with high BUN/Cr were more likely to be white, to be older, more likely to be on loop and potassium-sparing diuretics and had slightly lower hemoglobin levels. Although patients with high BUN/Cr were more likely to have diabetes, they were less likely to have hypertension. Notably, there was no difference in prevalence of any or >1+ proteinuria between groups (Table 2).

4.1. Proteinuria and mortality

In total, 23.3% of the population died during a median follow-up of 2.8 years. The presence of any proteinuria at baseline was associated with increased mortality (HR = 1.2; 95% CI, 1.1–1.4, $p = 0.001$), an association that persisted with adjustment for baseline eGFR (HR = 1.1; 95% CI, 1.01–1.3, $p = 0.034$). Although >1+ proteinuria was less common, it demonstrated a stronger relationship with mortality (HR = 2.5; 95% CI, 2.0–3.2, $p < 0.001$) that again remained after adjustment for baseline eGFR (HR = 2.1; 95% CI, 1.7–2.7, $p < 0.001$). Following adjustment for baseline factors significantly associated with proteinuria, BUN/Cr or mortality (age, race, sex, hypertension, diabetes, cerebrovascular disease, ischemic HF etiology, ejection fraction, New York Heart Association class, heart rate, systolic and diastolic blood pressure, beta blocker use, digoxin use, loop and potassium-sparing diuretic use, hematocrit, serum sodium, baseline eGFR and study drug) both any proteinuria (HR = 1.2; 95% CI, 1.1–1.3, $p = 0.006$) and >1+ proteinuria (HR = 1.9; 95% CI, 1.5–2.5, $p < 0.001$) remained similarly and significantly associated with increased mortality.