Renal dysfunction (RD) is a common finding in heart failure (HF) and has emerged as one of the most potent prognostic indicators in these patients. However, multiple different mechanisms capable of initiating a reduction in glomerular filtration rate (GFR) exist in HF, and the mechanism underlying the reduction in GFR likely has important prognostic and therapeutic implications. Unfortunately, limited progress has been made with respect to differentiation of these potential mechanistic subtypes of RD.

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The blood urea nitrogen/creatinine ratio (BUN/Cr) has been extensively used in clinical medicine for the differentiation of prerenal RD from intrinsic renal parenchymal disease. The discriminative ability of BUN/Cr is based on the intrarenal mechanisms governing tubular urea handling. In the setting of a prerenal stressor, such as dehydration, significant renal neurohormonal activation (ie, increases in vasopressin, renal sympathetic nerve activity, and the renin–angiotensin–aldosterone axis) causes a disproportionate reabsorption of urea compared with that of creatinine. Similarly, HF-induced RD has also traditionally been classified as a prerenal form of RD, and renal neurohormonal activation is hypothesized to represent a prominent mechanistic contributor to the genesis of this form of RD.

Given that most prerenal forms of RD are reversible if the appropriate treatment is instituted, it is plausible that some forms of HF-induced RD will also be reversible. The fact that elevated admission BUN/Cr is associated with a higher risk of hospital IRF suggests that this form of RD may be a discernible entity. However, this improvement seems to be largely transient, and RD, in the setting of an elevated BUN/Cr, remains strongly associated with death. Further research is warranted to develop strategies for the optimal detection and treatment of these high-risk patients.
improvement in renal function (IRF) seems to occur in up to 30% of acutely decompensated HF patients with their return to compensation supports this possibility. Given that an elevated BUN/Cr is often associated with reversible prerenal physiology, we hypothesized that an elevated admission BUN/Cr would identify patients with reversible HF-induced RD that would improve with treatment of their decompensated HF. However, given that IRF is transient in the majority of patients, we also hypothesized that, despite this potential reversibility, RD, in the setting of an elevated BUN/Cr, would still be associated with worsened survival. The primary aim of this study was to determine whether baseline BUN/Cr could identify patients with reversible RD and to validate, in the same population, our previous observations that RD in the setting of an elevated BUN/Cr is associated with substantially worsened survival.

Methods

Consecutive admissions from 2004 to 2009 to the cardiology and internal medicine services at the Hospital of the University of Pennsylvania with a primary discharge diagnosis of congestive HF were reviewed. Inclusion required an admission B-type natriuretic peptide level of >100 pg/mL within 24 hours of admission, a length of stay of 3 to 14 days, and availability of serum creatinine and BUN levels. There were 7 patients without admission serum BUN levels available who met all other inclusion criteria, accounting for the slightly lower number of patients in this cohort than the parent cohort from which it was derived. Patients on renal replacement therapy or those admitted to interventional cardiology services (to avoid confounding from contrast nephropathy) were excluded. In the event of multiple hospitalizations for a single patient, the first admission was retained. Post-discharge renal function was ascertained in the subset of patients with data available as previously described.

Estimated GFR (eGFR) was calculated using the 4-variable modified diet and renal disease equation. Unless otherwise noted, IRF was defined as a ≥20% increase at any time during the hospitalization and post-discharge worsening renal function (WRF) as a ≥20% decrease in eGFR from the discharge to the outpatient value, consistent with previously published studies of IRF and WRF. All-cause mortality was determined via the Social Security death index. 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. The study was approved by the institutional review board of the Hospital of the University of Pennsylvania.

Statistical Analysis

The primary goal of this analysis was to evaluate the association between admission BUN/Cr and IRF during treatment of acute decompensated HF. For the purposes of the primary analysis and unless otherwise specified, BUN/Cr was treated as a continuous covariate. Values reported are means±SD, 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 χ² was used to evaluate associations between categorical variables. Spearman correlation coefficients were used to examine statistical dependence between 2 variables. To facilitate interpretability of the descriptive statistics relating to BUN/Cr, this variable was dichotomized as ≥20 or <20 (in accordance with common clinical practice) for these analyses. Multivariable logistic regression analysis was performed to estimate the association between BUN/Cr and IRF after adjusting for potential confounders. Candidate covariates for the multivariable models were obtained by screening clinical characteristics for an association with IRF at P≤0.2. Using backward elimination, any covariate whose removal resulted in a change in the odds ratio (OR) for BUN/Cr ≥10% was retained in the final model. Additionally, any candidate variable associated with IRF with P<0.05 was retained in the model, regardless of its influence on the OR. Covariates that had a P>0.2, but a theoretical basis for potential confounding, were manually forced into and subsequently retained in the final model. Furthermore, covariates associated with mortality at P≤0.2 were also manually forced into (and retained in) the final model, to ensure the relationship between BUN/Cr and IRF was not driven by the greater disease severity in patients with either IRF or an elevated BUN/Cr. A total of 24 covariates were included in the first step of model building, and 17 variables were retained in the final model. ORs were reported for every 10 increase in BUN/Cr. Proportional hazards modeling was used to evaluate time-to-event associations with all-cause mortality. Candidate covariates entered in the model were those with univariate associations with all-cause mortality P≤0.2 and model building was done analogously to that described above for the logistic regression models. Hazard ratios (HRs) were also reported as per 10 increase in BUN/Cr. To examine the effect of BUN/Cr on the association between eGFR and mortality, Kaplan–Meier curves for death from any cause were plotted for the 4 combinations of groups between patients with and without an elevated BUN/Cr defined as a BUN/Cr in the highest compared with the lowest quartile (in accordance with previous studies) and those with and without significant RD (eGFR<45 mL/min/1.73 m²). Statistical significance was determined with the log-rank test. Stratum-specific HRs and 95% confidence intervals (CIs) were derived from proportional hazards modeling of the individual strata, and the significance of the interactions was formally assessed in models incorporating terms for the main effect of renal function, the main effect of BUN/Cr, and the interaction between these variables. Statistical analyses were performed using Stata 12.0 (Statacorp, College Station, TX), and statistical significance was defined as a 2-sided P value <0.05, with the exception of tests of interaction where significance was defined as a P value <0.1.

Results

Overall, 896 patients met the inclusion criteria. Thirty-one percent of the population (n=278) experienced IRF during hospitalization with a mean improvement in eGFR in eGFR in these patients of 43.7±27.2%. The remainder of the cohort experienced a mean improvement in eGFR from admission to the highest eGFR during hospitalization of only 5.3±6.7%. A detailed description of baseline characteristics, influence of treatment, and prognosis associated with IRF has previously been described.

The mean baseline BUN/Cr in the cohort was 18.6±7.7 with a median value of 17 and an interquartile range of 13.3 to 22.2. Baseline BUN/Cr demonstrated very weak correlations with both admission serum creatinine (r=0.071; P=0.03) and eGFR (r=0.18; P<0.001). Baseline characteristics of patients with and without a BUN/Cr ≥20 are shown in Table 1. Notably, patients with an elevated BUN/Cr were more likely to be white, to be older, and to have an ischemic cause for their HF. Markers of venous congestion were more prevalent in patients with an elevated BUN/Cr, including an elevated jugular venous pressure and presence of peripheral edema. Additionally, the elevated BUN/Cr group had multiple baseline indices consistent with greater HF disease severity, including lower baseline eGFR, serum sodium, hemoglobin, and systolic blood pressure, and a higher B-type natriuretic peptide.

The admission BUN/Cr was significantly associated with IRF (OR, 1.5 per 10 increase in BUN/Cr; 95% CI, 1.3–1.8; P<0.001) (Figure 1). The association between BUN/Cr...
and IRF was linear across values of BUN/Cr as evaluated graphically with a lowess smoother. Patients with higher BUN/Cr also had a significantly greater likelihood of continuing to meet criteria for IRF at the time of discharge (OR, 1.5; 95% CI, 1.2–1.8; \( P < 0.001 \)). The BUN/Cr remained associated with IRF after adjustment for baseline eGFR (OR, 1.4; 95% CI, 1.2–1.7; \( P < 0.001 \)) and baseline factors associated with IRF (age, race, hypertension, diabetes mellitus, ischemic HF pathogenesis, jugular venous distention, ejection fraction, systolic blood pressure, loop diuretic dose, angiotensin converting enzyme or angiotensin receptor blocker use, \( \beta \)-blocker use, spironolactone use, thiazide use, nitrate use, B-type natriuretic peptide level, serum sodium, and serum hemoglobin) (OR, 1.4; 95% CI, 1.1–1.8; \( P = 0.004 \)). Results were similar when comparing BUN/Cr ≥20 with BUN/Cr <20, the top BUN/Cr quartile versus the remainder of population, the top BUN/Cr tertile versus the remainder of population, and BUN/Cr above and below the median for both the adjusted and unadjusted analyses (Table 2). Admission BUN demonstrated a significant univariate association with IRF (OR, 1.02; 95% CI, 1.01–1.02; \( P < 0.001 \)). When both admission BUN and BUN/Cr were examined together in a regression model adjusted for admission eGFR, only BUN/Cr retained a significant relationship with IRF (BUN/Cr OR, 1.4; 95% CI, 1.09–1.82; \( P = 0.01 \); BUN OR, 1.0; 95% CI, 0.99–1.01; \( P = 0.93 \)).

In the overall population, BUN/Cr increased on average 16.6±40.2% from admission to discharge (\( P < 0.001 \)). Interestingly, there was not a significant difference in the degree of increase in BUN/Cr between patients that met...
crisis for IRF at discharge compared with those that did not (14.7±39.5% versus 17.0±40.3% increase; \( P = 0.50 \)). This lack of difference seemed to be predominantly driven by the fact that patients with IRF had a relatively larger improvement in serum creatinine (25.0% improvement) compared with their improvement in BUN (13.8% improvement), ultimately leading to a net worsening in the ratio.

**Baseline BUN/Cr and Post-Discharge Renal Function**

The incidence of post-discharge WRF (data available \( n = 452 \), 50.4% of the population) was 39.2%. Importantly, there was no significant difference between baseline BUN/Cr (18.3±7.4 versus 18.9±7.9; \( P = 0.2 \)) or IRF (30.4% versus 31.5%; \( P = 0.7 \)) in those patients with and without post-discharge data available. Patients with higher baseline BUN/Cr were more likely to experience post-discharge WRF (OR, 1.4 per 10 increase; 95% CI, 1.1–1.8; \( P = 0.011 \)). Notably, this association was unchanged after adjustment for admission eGFR (OR, 1.4 per 10 increase; 95% CI, 1.1–1.8; \( P = 0.016 \)), discharge eGFR (OR, 1.4 per 10 increase; 95% CI, 1.1–1.9; \( P = 0.006 \)), or the admission to discharge change in eGFR (OR, 1.4 per 10 increase in BUN/Cr; 95% CI, 1.1–1.8; \( P = 0.020 \)). Notably, there was not a significant difference in the strength of association between BUN/Cr and post-discharge WRF between patients that did or did not experience in-hospital IRF (interaction \( P = 0.96 \)). This relationship was not detectable for discharge BUN/Cr (OR, 1.1 per 10 increase; 95% CI, 0.9–1.6; \( P = 0.28 \)), a finding unchanged by adjustment for admission eGFR (\( P = 0.33 \)), discharge eGFR (\( P = 0.22 \)), or the change in eGFR (\( P = 0.30 \)).

**Baseline BUN/Cr, RD, and Mortality**

Forty-four percent of the population died during a median follow-up of 2.6 years. Baseline BUN/Cr was significantly associated with increased mortality in this population (HR, 1.8 per 10 increase; 95% CI, 1.6–2.0; \( P < 0.001 \)), an association that persisted when adjusted for baseline eGFR (Table 3). Adjusting for baseline characteristics, chronic medical conditions, medication use, and admission laboratory data did not eliminate the independent association of increasing BUN/Cr with mortality (Table 3). Admission eGFR was also significantly associated with mortality (HR, 1.1 per 10 mL/min per 1.73 m² decrease in eGFR; 95% CI, 1.1–1.2; \( P < 0.001 \)), an association which persisted after adjustment for baseline BUN/Cr (HR, 1.1 per 10 mL/min per 1.73 m² decrease in eGFR; 95% CI, 1.1–1.2; \( P < 0.001 \)) and baseline characteristics (HR, 1.1 per 10 mL/min per 1.73 m² decrease in eGFR; 95% CI, 1.0–1.1; \( P = 0.017 \)). Consistent with our previously published findings in other populations, there was significant effect modification by BUN/Cr on the association between eGFR and mortality (interaction \( P = 0.04 \)). Notably, in patients with a BUN/Cr in the top quartile, the risk of death associated with admission eGFR remained significant (HR, 1.2 per 10 mL/min per 1.73 m² decrease in eGFR; 95% CI, 1.1–1.3; \( P = 0.001 \)). However, in patients with a BUN/Cr in the bottom quartile, eGFR was no longer associated with death (HR, 1.0 per 10 mL/min per 1.73 m² decrease in eGFR; 95% CI, 0.97–1.1; \( P = 0.25 \); interaction \( P = 0.029 \)). Consistent with our previously published findings, this effect modification was strengthened by adjustment for baseline eGFR (OR, 1.0 per 10 mL/min per 1.73 m² decrease in eGFR; 95% CI, 0.9–1.1; \( P = 0.28 \)); discharge eGFR (OR, 1.1 per 10 mL/min per 1.73 m² decrease in eGFR; 95% CI, 1.1–1.3; \( P = 0.001 \)); and baseline characteristics (HR, 1.1 per 10 mL/min per 1.73 m² decrease in eGFR; 95% CI, 1.0–1.1; \( P = 0.017 \)).
by adjustment for baseline characteristics, including age, sex, race, hypertension, coronary artery disease, B-type natriuretic peptide, serum sodium, systolic blood pressure, heart rate, loop diuretic dose, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, β-blockers, digoxin, thiazide and spironolactone use, serum sodium, hemoglobin, B-type natriuretic peptide level, and admission eGFR.

Table 3. Association Between BUN/Cr and All-Cause Mortality

<table>
<thead>
<tr>
<th>Association</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.8 (1.6–2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for admission eGFR</td>
<td>1.7 (1.5–1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for baseline characteristics*</td>
<td>1.3 (1.1–1.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

BUN/Cr was analyzed as a continuous parameter and HR are per 10 increase in BUN/Cr. BUN/Cr indicates blood urea nitrogen/creatinine ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; and HR, hazard ratio.

*Adjusted for age, race, hypertension, diabetes mellitus, coronary artery disease, preserved ejection fraction, systolic blood pressure, heart rate, loop diuretic dose, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, β-blockers, digoxin, thiazide and spironolactone use, serum sodium, hemoglobin, B-type natriuretic peptide level, and admission eGFR.

The primary finding of this study is the strong association between an elevated admission BUN/Cr and significant improvement in kidney function during the treatment of acute decompensated HF. Even after adjustment for comorbidities known to impact renal function, as well as medications that influence GFR, an elevated BUN/Cr at admission continued to be strongly associated with IRF. However, the IRF observed after standard decompensated HF treatment was frequently transient, and RD in the setting of an elevated BUN/Cr remained strongly associated with reduced survival. These findings provide proof of concept that not only may prospective identification of potentially reversible forms of RD be possible, but also that this form of RD seems to represent, perhaps, the most prognostically important cardiorenal phenotype in HF.

Urea plays a fundamental and direct role in fluid and sodium homeostasis, processes tightly regulated by neurohormonal systems. 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 GFR, ultimately leading to an elevated BUN/Cr. However, with intrinsic renal parenchymal disease, the primary defect leading to RD is irreversible nephron loss rather than neurohormonal activation. As a result, the rate of urea clearance is reduced in parallel to GFR, resulting in a normal BUN/Cr. This neurohormonally mediated disassociation between urea reabsorption and glomerular filtration forms the basis for the widespread clinical application of BUN/Cr for the differentiation of prerenal RD from intrinsic renal parenchymal disease. Given the key role for neurohormones in the pathogenesis of both HF and reversible prerenal forms of RD, this physiology may represent the common thread linking the finding of reversibility and the increased risk for death.

We have previously reported that the majority of patients who experience IRF during the treatment of decompensated HF actually have post-discharge recurrence of the RD. Similar, in the current analysis, we found that an elevated admission BUN/Cr was also associated with an increased incidence of post-discharge WRF, independent of the discharge eGFR or changes in eGFR during hospitalization. These observations allow some speculation as to how BUN/Cr could identify a form of RD that is potentially reversible and also associated with significantly increased mortality. Because currently available HF treatments are not capable of increasing renal function to supranormal levels, for improvement in kidney function to be possible, reversible RD must be present at baseline (with the most likely pathogenesis being RD induced by severe HF). Given that patients experiencing IRF were likely sicker at baseline and the improvement in disease severity is largely transient, it is understandable how an elevated BUN/Cr could potentially be associated with reversible RD but also worsened survival. However, we have also previously reported that in the few patients who maintain IRF long term, there may actually be improved survival associated with the IRF. Although again speculative, this observation raises the possibility that strategies aimed at inducing and maintaining IRF could potentially lead to improved outcomes. Markers, such as
BUN/Cr, may allow the prospective identification of patients with the potential for IRF, facilitating interventional trials that can actually prove or disprove causality for these highly complex associations.

Despite the above promising proof-of-concept findings, BUN/Cr is a less than ideal measure of renal urea handling and is influenced by non-renal factors, such as diet and protein catabolism. Furthermore, creatinine-based estimates of GFR also have significant limitations secondary to factors such as the dependence of serum creatinine on muscle mass and tubular secretion. Recently, several novel renal biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), and kidney injury molecule 1 (KIM-1), have demonstrated high specificity in the detection of acute kidney injury. Furthermore, at present, the widely available filtration marker cystatin C offers the advantage of limited influence from lean body mass and tubular secretion. It is reasonable to hypothesize that given the strong signals demonstrable using a crude metric, such as BUN/Cr, the aforementioned renal biomarkers may provide superior discriminative ability.

Limitations

There are several limitations that must be considered when interpreting these results. First, given the retrospective study design, causality is impossible to demonstrate and residual confounding cannot be excluded. Physicians were not blinded to measures of renal function and, thus, may have altered treatment decisions in response to these data. Furthermore, given that proven methodology to detect and optimally treat reversible RD in this population was unavailable to the treating physicians, it is highly likely that some patients with reversible RD may have been refractory to the treatment they received (or possibly received treatment that led to no improvement or worsening in renal function) and, thus, did not experience IRF. This possibility may have led to a substantial underestimation of the magnitude of the association between BUN/Cr and reversible RD. Additionally, non-neurohumoral factors, such as diet and protein catabolism, that influence urea reabsorption may have introduced potential uncontrolled confounding. Given the slow equilibration time and nonrenal factors that influence serum creatinine, assessment of IRF based on creatinine-based eGFR may also have introduced bias. The analysis of post-discharge renal function has a large degree of missing data, which are likely missing not at random and, thus, may have significant bias inherent to the results. As a result of the above limitations, our findings should be considered hypothesis-generating and serve primarily to initiate further investigation.

Conclusions

In the setting of decompensated HF, an elevated BUN/Cr identifies patients likely to experience IRF, providing proof of concept that reversible RD may be a discernible entity. However, the improved kidney function observed following standard decompensated HF treatment seems to be largely transient and, perhaps as a result, RD in the setting of an elevated BUN/Cr remains strongly associated with worsened survival. Further research to develop methodology for the optimal detection and treatment of these high-risk patients is warranted with the goal of facilitating sustained improvements in renal function and potentially clinical outcomes.

Sources of Funding

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Disclosures

None.

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CLINICAL PERSPECTIVE

Renal dysfunction (RD) has emerged as one of the most potent risk factors for death in patients with heart failure (HF). In some patients, RD is a direct result of HF and potentially reversible. In others, the RD is primarily because of irreversible renal parenchymal disease, such as that caused by diabetes mellitus or hypertension. To date, methodology has not been identified that can differentiate reversible HF-induced RD from intrinsic RD. In this study, we investigated whether an elevated admission blood urea nitrogen/creatinine ratio, a marker often used to distinguish prerenal physiology from chronic kidney disease, could identify patients with reversible HF-induced RD. We found that decompensated HF patients with an elevated admission blood urea nitrogen/creatinine ratio had a significantly greater incidence of improvement in renal function with the return to compensation. Despite the improvement in these patients, recurrence of RD was common after discharge, and the greatest survival disadvantage clustered in patients with RD and an elevated admission blood urea nitrogen/creatinine ratio. These findings provide proof of concept that prospective identification of potentially reversible HF-induced RD is possible. Further research is warranted to develop strategies for the optimal detection and treatment of these high-risk patients.
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Meredith A. Brisco, Steven G. Coca, Jennifer Chen, Anjali Tiku Owens, Brian D. McCauley, Stephen E. Kimmel and Jeffrey M. Testani

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