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Renal biomarkers and outcomes in outpatients with heart failure: The Atlanta cardiomyopathy consortium

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ABSTRACT

Background/objectives: Cystatin-C and beta-2-microglobulin may be superior to serum creatinine, blood urea nitrogen (BUN), or estimated glomerular filtration rate (eGFR) in patients hospitalized with heart failure (HF). We compared these renal markers in ambulatory HF patients.

Methods: We prospectively evaluated the association of baseline renal markers and eGFR (by 4 different formulas) with (1) the composite of death or HF-related hospitalization and (2) rates of hospitalizations and emergency department (ED) visits in 166 outpatients with HF (57.3 ± 11.6 years; 57.2% white, 38.6% black, median left ventricular ejection fraction 27.5% [17.5, 40.0]).

Results: After a median of 3.9 years, 63 (38.0%) patients met the composite endpoint. There were 458 hospitalizations (177 [38.6%] for HF) and 209 ED visits (51 [24.4%] for HF). Cystatin-based eGFR most consistently predicted (1) the composite endpoint (highest-to-lowest tertile adjusted hazard ratio [HR] 4.92 [95% CI 2.07–11.7; $P < 0.001$]); and (2) hospitalization rates, including HF hospitalizations (highest-to-lowest tertile, adjusted relative rate 5.24 [95% CI 1.61–17.01; $P = 0.006$]). Serum creatinine alone was a strong predictor of the composite endpoint (highest-to-lowest tertile, adjusted HR 3.20 [95% CI, 1.51–6.78; $P = 0.002$]). Only the highest tertile of BUN was associated with rates of ED visits.

Conclusions: In outpatients with HF, cystatin-based eGFR provides consistent prognostication across outcomes, except ED visits. Serum creatinine is an adequate prognosticator of death or HF hospitalization.

Declining mortality trends and changing population structure has led to a dramatic increase in the prevalence of heart failure (HF), with some estimates as high as 5.7 million persons in the US [1]. More than 1 million HF hospitalizations occurred in 2010 [2]. Total cost of HF was over $30 billion in 2012 [3], whereas this cost is estimated to increase by 200% by 2030 [2]. Most HF cases affect older adults [4–6], often accompanied by comorbidities that complicate management [7,8]. The coexistence of HF and renal dysfunction, often termed as "cardiorenal syndrome", is present in 20%–57% of patients with HF [9–11]. This syndrome has been difficult to precisely define [12]. The bidirectional relationship between the heart and the kidney in HF is not completely understood. The compromised renal function in HF is attributed to poor kidney perfusion, venous congestion, and neurohormonal activation [13]. Renal dysfunction may also act as a pathogenic factor in HF through salt and fluid retention with resulting increased preload and afterload that may worsen cardiac function further [14]. Age, hypertension, and diabetes may act as unifying factors linking HF with chronic kidney disease [15]. Regardless of its etiology, renal dysfunction in HF is a marker of poor prognosis, with increased risk of death and hospitalization. However, these data come mainly from acute HF cohorts [9,11,16–22]. Few studies have evaluated the impact of renal function in patients with ambulatory, well-compensated HF [23–25].

Renal dysfunction in patients with HF can identify patients at risk for higher healthcare utilization rates and worse outcomes. However, because direct assessment of the glomerular filtration rate (GFR) is clinically impractical, we use circulating molecules as surrogates of renal function, all of which have been shown to be associated with outcomes in HF [21,26–32]. Examples include serum creatinine, blood urea nitrogen (BUN), BUN-to-creatinine ratio, estimated GFR (eGFR), and, more recently, beta-2 microglobulin (B2μ) [33,34] and cystatin proteinase inhibitor (cystatin C) [26,28,30,31,35–44]. The prognostic value of traditional and novel markers of renal function in HF is highly dependent on outcome definition, timeframe, and selected covariates, and thus, it is difficult to compare between studies [45]. The recent focus on

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healthcare costs associated with HF has led to consideration of healthcare utilization rates as an important HF outcome. Beyond increased risk for mortality, higher healthcare utilization rates can potentially identify a subset of patients that may benefit from more intensive management [46]. However, data on the association of renal function markers with healthcare utilization rates in outpatients with HF are limited.

In this analysis, we used data from a prospective cohort study of HF outpatients to assess whether cystatin C and B2μ can improve prediction of clinical events and healthcare utilization rates risk over serum creatinine, BUN, and eGFR calculated by different equations.

1. Methods

1.1. Study population

The Atlanta Cardiomyopathy Consortium (TACC) is a prospective cohort study in outpatients with HF from 3 university-affiliated hospitals in the greater metropolitan Atlanta area. Inclusion criteria include age > 18 years, able to understand and sign informed consent and participate, and a diagnosis of HF with either reduced or preserved left ventricular ejection fraction (LVEF). The diagnosis of HF with preserved LVEF required, in addition to clinical criteria, a B-type natriuretic peptide level > 200 pg/dl and/or echocardiographic evidence of diastolic dysfunction [47,48]. Exclusion criteria included congenital heart disease, previous heart transplantation or on currently awaiting transplant, implanted left ventricular assist device (LVAD), known cardiac infiltrative disease (e.g., amyloidosis), previous other solid organ transplantation, and end-stage HF requiring outpatient continuous inotrope infusion. All patient data and blood samples were collected during dedicated study visits. The Emory University institutional review board has approved this study and all patients have signed informed consent. Serum cystatin C and B2μ at baseline were available in 166 patients, providing the analysis cohort for this study.

1.2. Measurement of biomarkers

Blood samples were centrifuged for 10 min at 4 °C and supernatant was transferred to cryovials and stored at −80 °C. For B2μ, we used the Quantia B2M latex-enhanced immunoturbidimetric assay on an Architect ci8200 platform (Abbott Laboratories, Abbott Park, IL). The limit of quantification (the lowest measurable concentration with a within-run coefficient of variation [CV] below 20% and recovery within ±20% of expected value) for B2M was 0.250 mg/L and the limit of detection was 0.046 mg/L. The total CV of the assay is <6%. Cystatin C was determined with the Diazyme latex-enhanced immunoturbidimetric assay (Diazyme Laboratories, Poway, CA), which has a sensitivity of 0.068 mg/dL, an extended linear range from 2.0 to 8.0 mg/dL, and intra and inter-assay CV <5%. Creatinine and BUN were measured by clinically approved assays on the same platform. The intra- and inter-assay CVs were 0.9% and 0.8% for BUN and 1.7% and 1% for creatinine. Also, we considered the ratio of BUN to creatinine, which has been shown to have prognostic utility in patients with HF and renal dysfunction [49].

1.3. Estimation of eGFR

For estimation of eGFR, we considered the Modification of Diet In Renal Disease ($eGFR_{MDRD}$) [50] equation and the creatinine ($eGFR_{CKD\text{-}Epi}$) [51]; cystatin C ($eGFR_{Cys}$) [52]; and creatinine cystatin C based ($eGFR_{Cr\text{-}Cys}$) [53] equations from the Chronic Kidney Disease Epidemiology Collaboration group. We did not consider the Cockcroft–Gault equation, as it is practically obsolete.

1.4. Assessment of outcomes and endpoints

Every six months, the patients were contacted to assess medication changes, procedures, new diagnoses, hospitalizations, and emergency department (ED) visits. Mortality was ascertained through medical records, information from family members, and Social Security Death Index query. Hospitalization data were obtained from electronic medical records, outpatient notes from any encounter for admissions to outside hospitals, and direct patient inquiry during follow-up.

The primary endpoint was the composite of death or hospitalization for HF, on a time-to-first-event basis. The secondary endpoints were the rates of hospital admissions and ED visits. We have divided admissions and ED visits into cardiovascular and noncardiovascular. We have further subdivided cardiovascular admission and ED visits into HF-related and non-HF-related. The reasons for admissions and ED visits have been individually verified by chart review.

1.5. Statistical analysis

Descriptive data are presented as mean ± standard deviation or median (25th, 75th percentile) for continuous variables and N (%) for categorical variables. Renal biomarkers and eGFR were divided into tertiles for unbiased categorization and prognostic head-to-head comparison. We used the lowest tertile as reference category for biomarkers and the highest tertile (better renal function) as reference category for eGFR. Based on clinical rationale, we used the middle tertile as reference category for BUN to creatinine ratio. We used Cox proportional hazards models for the primary endpoint (death or HF hospitalization). The proportional hazards assumption was tested with the Schoenfeld residuals and was met across all models tested. We modeled rates of hospitalizations and ED visits (the secondary endpoint) using negative binomial regression models, which allow for overdispersion (i.e. clustering of events within certain patients) and have been previously validated for these outcomes [54]. Unadjusted and adjusted hazard ratios (HR) for Cox models and rate ratios (RR) for negative binomial regression models were calculated for each renal biomarker and eGFR equation. Based on previous literature, estimates were adjusted in multivariable models for age, gender, race, systolic blood pressure, hemoglobin, presence of diabetes mellitus, LVEF, etiology of HF (ischemic vs. nonischemic), New York Heart Association (NYHA) class, and medical therapy. All statistical analyses were conducted using STATA 13.1 (StataCorp, College Station, Texas).

2. Results

2.1. Baseline characteristics

The mean age of patients (N = 166) was 57.3 ± 11.6 years. Of these, 64.5% were men, 57.2% white, and 38.6% black. The median LVEF was 27.5% (interquartile range, 17.5 to 40.0); 19.3% of patients had LVEF >40%. Etiology of HF was ischemic in 40.4% of patients. The baseline characteristics of the study participants, including median serum levels of renal markers and eGFR calculated with the most commonly used equations are presented in Table 1.

2.2. Renal markers and composite endpoint (death or hospitalization for heart failure)

Over a median of 3.9 (3.6, 4.0) years of follow-up (total: 580 person-years), 29 patients died and an additional 34 were hospitalized for HF (composite endpoint met by 38.0%). The cumulative incidence of the composite endpoint is shown in Fig. 1. Among renal biomarkers, creatinine showed the strongest association with the composite endpoint, Table 2. In models adjusting for demographics, LVEF, NYHA class, systolic blood pressure, hemoglobin, diabetes mellitus, HF etiology (ischemic vs. nonischemic), and medical therapy, the highest-to-lowest tertile HR