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Bryan S. Overcarsh Date

Renal Biomarkers and Outcomes in Outpatients With Heart Failure

By

Bryan Scott Overcarsh
Master of Public Health

Epidemiology

_____

William McClellan, MD
Committee Chair

_____

Andreas Kalogeropoulos, MD, PHD
Committee Member

Renal Biomarkers and Outcomes in Outpatients With Heart Failure

By

Bryan Scott Overcarsh

BA, BS
University of Georgia
2008

Thesis Committee Chair: William McClellan, MD

An abstract of
A thesis submitted to the Faculty of the
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Master of Public Health
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Abstract

Renal Biomarkers and Outcomes in Outpatients With Heart Failure
By Bryan Overcarsh

Introduction: Cystatin C and beta-2 microglobulin (B2M) may be superior renal markers compared to creatinine (Cr), blood urea nitrogen (BUN), and calculated glomerular filtration rate (GFR) in patients with acute decompensated heart failure but data in stable heart failure patients is limited.

Methods: We evaluated the association of baseline tertiles of Cr, BUN, BUN/Cr ratio, GFR (by MDRD formula), Cys-C, and B2M with clinical events and health care resource utilization (HCRU) rates in 159 outpatients (age 57.3±11.7; 103 (65%) men; 92 (58%) white; black; EF 29.5±15.2) enrolled in a prospective cohort study.

Results: Over 42±12 months (total: 560 person-years), there were 33 (20.7%) clinical events (27 deaths, 4 transplants, 2 ventricular assist device implantations), 445 all-cause admissions (170 [38.2%] for HF), and 207 emergency department (ED) visits. Among renal markers, Cr had the strongest association with clinical events, with a highest vs. lowest tertile hazard ratio of 7.30 (95% CI 1.58-33.70; P 0.01) in models adjusted for demographics (age, race, gender), LVEF, NYHA class, systolic blood pressure, serum sodium, etiology (coronary artery disease, other), and medical therapy (beta blockade, ACE inhibitor, Angiotensin receptor blocker). Cr also had the strongest association with HCRU rates. In adjusted models, the highest vs. lowest Cr tertile rate ratio was 3.02 (95% CI 1.75- 5,24; P<0.001) for all-cause admissions; 5.2 (95% CI 1.71-15.89; P<0.005) for HF admissions; and 2.89 (95% CI 1.37-6.09; P=0.005) for ED visits.

Conclusion: In outpatients with heart failure, serum Cr may be prognostically superior to other traditional and novel markers of renal function.

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Chapter 1

Literature Review

Heart failure (HF) is characterized by the inability of the heart to meet the demands of the body and is a major public health problem. It is estimated that 550,000 new cases of HF are diagnosed annually. Most of these cases affect the elderly, with an annual incidence of 10 per 1000 persons after age 65, increasing to more than 40 per 1000 persons older than 85 years (1-3). The incidence of heart failure appears to be relatively stable, but declining mortality and changing population structure has led to a dramatic increase in heart failure prevalence, with some estimates as high as 5.7 million persons in the United States alone (4). Heart failure is the most common discharge diagnosis among Medicare beneficiaries (5, 6). The five-year mortality of heart failure is approximately 50% and the rate of hospitalization in the last year of life is 80% with 1 million hospitalizations occurring in 2010 (6-8) The costs of these hospitalizations are high, estimated to be above $17,000 per hospitalization among adults under age 64 (9). The resulting total cost of heart failure is estimated to be $34.4 billion annually (10).

Renal impairment is present in 20-57% of patients with chronic heart failure (11-13). The coexistence of heart failure and renal dysfunction is labeled the cardiorenal syndrome. This syndrome has been difficult to precisely define, with multiple coexisting definitions leading to a recent consensus definition as a "complex disorder whereby dysfunction in one organ may induce acute or chronic dysfunction in the other" (14). Although the bidirectional relationship between the heart and the kidney in heart failure is not completely understood, compromised renal function in heart failure is attributed to poor kidney perfusion, venous

congestion, and the use of diuretics as treatment for fluid overload. Renal dysfunction may also act as a pathogenic factor in heart failure by leading to salt and fluid retention with resulting increased preload and afterload that may worsen cardiac function in heart failure (15). Additionally, age, hypertension, and diabetes may act as unifying factors that associate heart failure with CKD (16). Regardless of its etiology, the presence of renal dysfunction in heart failure is known to be a marker of poor prognosis with an increased risk of re-hospitalization and death (11, 13, 17-19).

Early identification of renal dysfunction in patients with heart failure is therefore an important goal, as it can identify patients at risk for increased healthcare utilization and worse outcomes. Direct assessment of GFR using inulin clearance is cumbersome and clinically impractical. This has led to the development of a number of naturally circulating molecules that can be used as biomarkers of renal function and that have each been shown to be associated with outcomes in heart failure patients. The term biomarker can be used to describe the results of routine lab tests, imaging studies, tissue biopsies, physiological tests, and circulating molecules but this review will be limited to circulating proteins used to identify renal dysfunction. Examples of renal biomarkers include serum creatinine (Cr), Cystatin proteinase inhibitor (cystatin-c), beta-2 microglobulin (B2M) as well as calculated values derived from these proteins.

Serum creatinine is a traditional biomarker used in the assessment of renal function. Decreased renal function is associated with increased cardiac risk even at modest elevations of serum creatinine (>1.4 mg/dL) (20). Serum Creatinine alone however is not recommended as a sole measure of renal function as it can be affected by patient age, sex, race, muscle mass, and diet (21). Several formulas are available to estimate glomerular

filtration rate using levels of circulating creatinine in combination with age, race, sex, and other factors that affect GFR. These include the Cockroft-Gault and MDRD equations. In heart failure patients, body composition can vary greatly from the populations in which these formulas were derived. The MDRD formula has been shown to be more precise than the Cockroft-Gault and modified MDRD estimates of GFR in heart failure patients although all formulas overestimated the lower ranges of GFR and underestimated the upper ranges of GFR (22). In comparison to directly measured GFR, 24-hour creatinine clearance and the MDRD equation has prognostic value for cardiovascular outcomes (17).

Cystatin proteinase inhibitor (Cystatin C) is a marker of glomerular function and an alternative to serum creatinine for the estimation of GFR. Cystatin C is a low molecular weight protein that is produced by all nucleated cells at a constant rate (23). Cystatin C is freely filtered by the glomerulus and is thus a marker of GFR (24). Compared to creatinine, serum concentrations of Cystatin C are less influenced by factors other than GFR such as muscle mass, age, race, and sex (25). As such, Cystatin C has attracted study as a possible risk predictor in patients with heart failure. Cystatin C has been reported in several studies to be a prognostic indicator in patients with systolic heart failure (26-28). Additionally, Cystatin C is also reported to be more closely associated with all cause mortality and cardiovascular events in the elderly than is creatinine (29). The CKD-Epi cystatin C formula estimates GFR using serum cystatin C. The CKD-Epi cystatin C formula was developed by pooling several cohorts and comparing cystatin c with GFR measured by iothalamate or chromium-51-EDTA. (30).

Serum beta-2 microglobulin (B2M) is a low molecular weight protein component of the HLA antigen that is nearly completely filtered by the glomeruli, reabsorbed by the proximal tubule, and can serve as an endogenous marker of GFR (31, 32). Serum B2M has been shown to be an independent predictor of all cause mortality in the elderly population (33). B2M has also been shown to be a prognostic indicator in patients with acute heart failure and serum creatinine less than 3 mg/dL (34). As it is a relatively new marker, there is no clinically normal range that is widely accepted.

Despite the proliferation of biomarkers that may prove useful in heart failure, only B-type natriuretic peptide (BNP) is widely used in the clinical setting. The development of new biomarkers can be conceptualized as proceeding in phases proposed by the American Heart Association:

1. Proof of concept: Do marker levels differ between subjects with and without outcome?
2. Prospective validation: Does the marker predict development of future outcomes in a prospective cohort or nested case-cohort/case-cohort study?
3. Incremental value: Does the marker add predictive information to established risk markers?
4. Clinical utility: Does the risk marker change predicted risk sufficiently to change therapy?
5. Clinical outcomes: Does use of the novel risk marker improve clinical outcomes, especially when tested in a randomized clinical trial?

6. Cost-effectiveness: Does use of the marker improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?

(35)

Unfortunately many biomarkers never make it past stage 3, as it is difficult to prove that novel biomarkers provide added benefit to the use of traditional biomarkers (36). Beyond the use of BNP for diagnostic purposes, there are few widely used applications for biomarkers in heart failure. The statistical value of existing and novel markers of renal function in heart failure patients is highly dependent on the outcome definition, timeframe, and selected covariates and is thus difficult to compare among studies (36). In heart failure research, this can be partly attributed to changes over time in the definition of heart failure, which has grown to include patients with preserved ejection fraction making comparisons between studies difficult. Additionally, pertinent outcomes have expanded from CV events to include healthcare utilization as measured by hospitalizations and emergency room visits. Selected covariates vary among studies based on the criteria for selection. Smaller studies are less likely to identify significant confounding variables using selection methods, and literature based selection of covariates is inherently variable among studies.

Incremental value is difficult to evaluate because it is difficult to define. Beyond the difficulties noted above in selecting a population, outcome, and meaningful covariates there is also the problem of evaluating the increment in prediction added by a new marker. Many studies have simply reported the new biomarker's statistical properties in a model consisting of arbitrarily defined covariates. Reporting the relative risk as well as p values and c statistics

at a minimum has been used to suggest that a new marker provides a statistical improvement over previously measured variables.

Risk reclassification is a newer method that has rapidly become the standard for evaluating new biomarkers (37). Risk Reclassification evaluates the change in estimated risk using the new marker as compared to some baseline model. If the new marker results in more patients being classified as higher risk who experience and event and more patients classified as lower risk who do not experience an event as compared to the baseline model. This approach has been especially useful in cardiovascular risk prediction where new markers can be compared against an accepted risk score such as the Framingham Risk Score. Risk reclassification implies an initial meaningful risk classification. In HF there is no widely accepted risk score used to stratify patients.

In order to promote a new biomarker into practice it must be used in a consistent manner in order to be compared to existing markers. This analysis will seek to assess whether either of the novel markers of renal function cystatin-C and beta-2 microglobulin predict cardiac outcomes better than serum creatinine and estimated GFR in a single prospective cohort of patients with stable heart failure.

Chapter 2
Manuscript

Abstract

Introduction: Cystatin C and beta-2 microglobulin (B2M) may be superior renal markers compared to creatinine (Cr), blood urea nitrogen (BUN), and calculated glomerular filtration rate (GFR) in patients with acute decompensated heart failure but data in stable heart failure patients is limited.

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Conclusion: In outpatients with heart failure, serum Cr may be prognostically superior to other traditional and novel markers of renal function.

Background and Rationale

The coexistence of heart failure and renal dysfunction is labeled the cardiorenal syndrome. This syndrome has been difficult to precisely define, with multiple coexisting definitions leading to a recent consensus definition as a "complex disorder whereby dysfunction in one organ may induce acute or chronic dysfunction in the other" (14). Although the bidirectional relationship between the heart and the kidney in heart failure is not completely understood, compromised renal function in heart failure is attributed to poor kidney perfusion, congestion, and the use of diuretics as treatment for fluid overload. Additionally, age, hypertension, and diabetes may act as unifying factors that associate heart failure with chronic kidney disease (CKD) (16).

Regardless of its etiology, the presence of renal dysfunction in heart failure is known to be a marker of poor prognosis (17). Early identification of renal dysfunction in patients with heart failure is therefore an important goal, as it can identify patients at risk for worse outcomes and increased healthcare utilization. Direct assessment of the glomerular filtration rate (GFR) is clinically impractical and this has led to the identification of a number of naturally circulating molecules that can be used as biomarkers of renal function. The prognostic value of existing and novel markers of renal function in heart failure patients is highly dependent on the outcome definition, timeframe, and selected covariates and is thus difficult to compare among studies (36). This purpose of this report is to assess the extent to which two of these biomarkers, cystatin-C and B2 microglobulin, improve the prediction of cardiac outcomes in a prospective cohort of patients with stable heart failure.

Methods

Study dataset

The Atlanta Cardiomyopathy Consortium (TACC) is a prospective cohort study enrolling outpatients with HF from three university-affiliated hospitals in the greater metropolitan Atlanta area. Inclusion criteria included age >18 years, able to understand and sign written 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 diagnosis of HF, elevated B-type natriuretic peptide level >200 pg/dl and/or an echocardiogram evidence of diastolic dysfunction.(38) Exclusion criteria included congenital heart disease, previous heart transplantation or on currently awaiting transplant, known cardiac infiltrative disease (e.g., amyloidosis), previous other solid organ transplantation, and end-stage HF requiring outpatient continuous inotrope infusion.

Assessment of Outcomes

Every six months, the patients are contacted to assess medication changes, procedures, new diagnoses, and hospitalizations. Mortality data are collected through medical record review, information from family members, and Social Security Death Index query. Hospitalization data are obtained from electronic health records review, outpatient notes from any specialty encounter for any admission to an outside hospital, and direct patient inquiry during follow-up. The Emory University institutional review board approved this study.

The TACC database includes 333 patients. Serum beta-2 microglobulin and cystatin c were measured for the first 177 patients enrolled and then discontinued due to cost. Of these 177 patients, 11 were excluded from the final analysis for missing serum creatinine, 5 were

excluded for missing NYHA class, 1 was excluded for missing LVEF, and 1 excluded for missing baseline systolic blood pressure, leaving 159 patients for the analysis. Renal biomarkers were divided into tertiles for an unbiased categorization of continuous variables. For beta2-microglobulin tertile cut points were <2.1, >2.8; for creatinine <1.1, >1.3; and cystatin-c <1.12, >1.54. The primary outcome was defined as a composite of death, need for left ventricular assist device, and urgent heart transplant. Healthcare utilization was defined as any hospital admission, any ED visit, and heart failure-specific admission or ED visit as determined by chart review.

Statistical analysis

Descriptive analysis is presented as mean ± standard deviation for continuous variables or N (%) for categorical variables.

Potential confounding variables controlled for included: demographics (age, race, gender), LVEF, NYHA class, systolic blood pressure, serum Na, etiology (coronary artery disease, other), and medical therapy (beta blockade, ACE inhibitor, angiotensin receptor blocker).

Cox proportional hazard models were used to conduct time-to-event analysis. The proportional hazards assumption was tested visually using log-log curves and by goodness of fit testing using Pearson correlation coefficients (**Appendix A**). Unadjusted hazard ratios were calculated for each of the study variables using cox proportional hazards regression. Estimates were then adjusted for patient age, gender, race, systolic blood pressure, serum sodium, LVEF, New York Heart Association class, and medical therapy with ACE inhibitors or beta blocking agents. Likelihood ratio tests were performed. Colinearity was assessed

using the variance inflation factor. The Harrell C-index was calculated with a 95% confidence interval based on the method described by Pencina and D'Agostino (39).

Poisson models were used to characterize healthcare utilization. The distribution of total hospitalizations and total emergency room visits showed evidence of over dispersion, and thus a negative binomial regression was used to estimate incidence rate ratios (**Appendix B**). This estimate was adjusted for demographics (age, race, gender), LVEF, NYHA class, systolic blood pressure, serum sodium, etiology (coronary artery disease, other), and medical therapy (beta blockade, ACE inhibitor, angiotensin receptor blocker). Results are reported as incidence rate ratios. Likelihood ratio tests were performed to determine the significance of model fit improvement over base model with the addition of the study variables.

Statistical analysis was done with SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 177 patients in the TACC database with measured serum B2M and cystatin-c, 11 were excluded from the analysis due to missing serum creatinine, 5 were excluded for missing NYHA class, 1 was excluded for missing LVEF, and 1 excluded for missing baseline systolic blood pressure. The average age of the remaining 159 patients was 57.34±11.7 years. Of these patients, 103 (65%) were male, and 92 (58%) were Caucasian. The average LVEF was 29.5% ± 15.2%, and the average NYHA class was 2.1±0.6. There were a total of 33 events (27 deaths, 2 LVAD implantations, 4 heart transplants) over 560 person-years of

follow up. The average length of follow up was 3.5 years with a standard deviation of 12 months. Baseline characteristics of the study participants are presented in Table 1.

Baseline tertiles of serum creatinine showed the strongest unadjusted association with clinical events with the highest vs. lowest tertile hazard ratio of 12.84 (95% CI 2.99-55.15; P<0.001). In models adjusted for demographics (age, race, gender), LVEF, NYHA class, systolic blood pressure, serum Na, etiology (coronary artery disease, other), and medical therapy (beta blockade, ACE inhibitor, Angiotensin receptor blocker) the highest vs. lowest tertile hazard ratio for creatinine was 7.30 (95% CI 1.58-33.70; P 0.01). The adjusted hazard ratio for highest versus lowest tertile of calculated GFR by the MDRD equation was 3.98 (95% CI 1.36-11.62; P 0.01). Hazard ratios for other renal biomarkers failed to meet statistical significance. Addition of the study variables to the base model did not result in large changes in the Harrell C-Index. These results are presented in Table 2.

In negative binomial Poisson models adjusted for demographics, LVEF, NYHA class, systolic blood pressure, serum sodium, HF etiology, and medical therapy, tertiles of all tested biomarkers of renal function were significantly associated with total hospitalizations. Tertiles of creatinine had the largest risk ratios with middle vs. lowest tertile risk ratio of 2.21 (95% CI 1.4-3.6; P<0.001) and a highest vs. lowest tertile risk ratio of 3.03 (95% CI 1.8-5.2; P<0.001). The risk ratio for highest vs. lowest tertiles of creatinine was 5.2 (95% CI 1.71-15.89; P<0.005) for HF admissions and 2.89 (95% CI 1.37-6.09; P=0.005) for ED visits. These data are shown in Figure 1.

Discussion

This study presents a comparison of several biomarkers of renal function that are strongly associated with adverse outcomes in a cohort of outpatients diagnosed with heart failure. When compared to a number of novel and traditional renal biomarkers, baseline tertiles of serum creatinine had the strongest association with clinical events and healthcare utilization. We observed that tertiles of serum creatinine are more strongly associated with the composite outcome (death, LVAD implantation, or transplant) than serum cystatin C and serum B2M, and either the MDRD or CKD-Epi cystatin C estimated GFR equation. Tertiles of creatinine were also the only study variable other than tertiles of GFR to achieve statistical significance in this sample and when compared to GFR, the effect size of creatinine was much larger with a highest vs. lowest hazard ratio of 7.30 compared to 3.98 for MDRD GFR.

Tertiles of creatinine also had the strongest association with all cause hospitalizations, and all cause ED visits. The difference was especially pronounced in relation to total ED visits, with creatinine being the only statistically significant predictor of the renal biomarkers we compared. All of the studied biomarkers of renal function were statistically significantly associated with all cause hospitalizations, but serum creatinine had the largest risk ratios. In terms of HF-specific hospitalizations, all renal biomarkers were statistically significantly associated with hospitalization. Serum cystatin c had the largest risk ratio for the middle tertile versus lowest tertile, but serum creatinine had the largest risk ratio for the highest versus lowest tertile.

The presence of renal insufficiency in heart failure is known to be associated with adverse outcomes in HF patients. Given the theoretical advantages of cystatin C and estimated GFR over serum creatinine in estimating renal function among patients with heart failure the superior association of serum creatinine with outcomes was unexpected. This study used a single population of heart failure patients to evaluate the ability of 5 renal biomarkers to predict death, heart transplant, and LVAD implantation. All 5 markers were divided into tertiles in order to create an unbiased classification and allow for comparison among biomarkers some of which do not have agreed upon clinical ranges. It is possible that for some of the same reasons that serum creatinine is a suboptimal measure of renal function in heart failure patients it performed well as a prognostic indicator. After controlling for age, gender, race, medical therapy, etiology, LVEF, NYHA class, SBP, and serum sodium it may be the sickest patients who have elevations in serum creatinine in comparison to cystatin c in spite of their decreased muscle mass and increased volume of circulation. Additionally, as a breakdown product of muscle, it is possible that elevations of serum creatinine in heart failure may be associated with additional pathophysiologic derangements beyond GFR and thus be a more inclusive marker of disease severity in heart failure.

Recent advances in basic science have led to a large body of circulating molecules that hold promise to refine the prognosis of patients with heart failure. Unfortunately many biomarkers stagnate as it is difficult to prove that novel biomarkers provide added benefit to the use of traditional biomarkers (36). This can be partly attributed to changes over time in the definition of heart failure, which has grown to include patients with preserved ejection fraction making comparisons between studies difficult. Previous studies of renal dysfunction and heart failure have largely focused on patients with acute heart failure, and typically

reported smaller effects of creatinine on mortality using a variety of stratifications of serum creatinine (40).

In two recent studies of chronic heart failure cystatin C outperformed estimated GFR (41) and serum creatinine (28). Our study differs from these in that our adjusted cox model takes into account the baseline severity of heart failure as described by both the LVEF and by the NYHA class in addition to demographic and medical confounders. Our population also differed in that patients were more likely to be on appropriate medical therapy (ACE inhibitor and beta blocker) were 9 years younger on average, and less likely to have a history of coronary artery disease. The different population studied may account for some of the differences between ours and other studies.

Many current investigations into cardiac biomarkers employ risk reclassification as an improvement over incremental c statistic (37). This method first requires a meaningful risk classification, which does not exist for mild to moderate heart failure as evidenced by the wide variety of models in the heart failure literature (36). The Seattle Heart Failure Model is an accepted method of risk stratification in heart failure, but was derived from a sicker cohort of patients with mostly reduced ejection fraction (42). For these reasons, risk reclassification was not pursued in this study.

Because serum creatinine is readily available in all hospital labs its relative value as a prognostic indicator in stable heart failure is significant. Additionally the availability of creatinine should also enable additional larger multisite studies that could provide a more definitive answer as to creatinine's value relative to other biomarkers of renal function. While

serum creatinine remains a suboptimal measure of renal function, its value in outpatients with heart failure may extend beyond a characterization of their renal function to an independent marker of disease severity that provides more information than GFR alone.

This study is limited by the small number of subjects (159) and the low number of primary events (33) although the event rate was 20%. Hazard ratios are unstable due to the small number of events, resulting in hazard ratios much larger than have been observed in larger cohorts. Despite this limitation, the direction of effect is consistent with previously reported associations between renal function and cardiac events in heart failure. Creatinine is already used widely in clinical practice, and may correlate with some outcomes because it is used in clinical decision-making. This is less likely in the case of the primary outcome (death, LVAD implantation, transplant) than for hospitalizations, which involve more clinical judgment and factors unrelated to disease biology. Additionally we have used baseline levels of renal markers, and the change in levels of these markers over time might be more informative about disease progression. Healthcare utilization is a difficult outcome to model because it may depend as much on unmeasured social factors such as insurance status and health literacy as on biological measures of disease.

In conclusion, among outpatients with heart failure serum creatinine may be prognostically superior to other traditional and novel markers of renal function in predicting cardiac events and healthcare utilization. Further studies should be undertaken using larger cohorts, as well as serial measurements to determine whether changes in renal biomarkers could be more informative than baseline measurements.

Table 1. Baseline Patient Characteristics (N= 159)

Age	**57.34±11.70**
Male	103 (65%)
Caucasian	92 (58%)
NYHA class	2.1±0.6
Left Ventricular Ejection Fraction, %	29.5±15.2
Ischemic Heart Disease	64 (40%)
Systolic Blood Pressure	110±17
Serum Sodium, mEq/L	138.5±2.6
Serum Creatinine, mg/dL	1.4±1.2
GFR (MDRD)	77.1±23.6
Serum Beta-2 Microglobulin	2.9±1.6
Serum cystatin-C	1.43±0.57
B-type Natriuretic Peptide, ng/mL	175.5 (66.5, 610.0)
Biventricular Pacemaker and/or Defibrillator, n (%)	111 (70%)
ACE Inhibitor or Angiotensin Receptor Blocker, n (%)	129 (81%)
Beta-Blocker, n (%)	150 (94%)

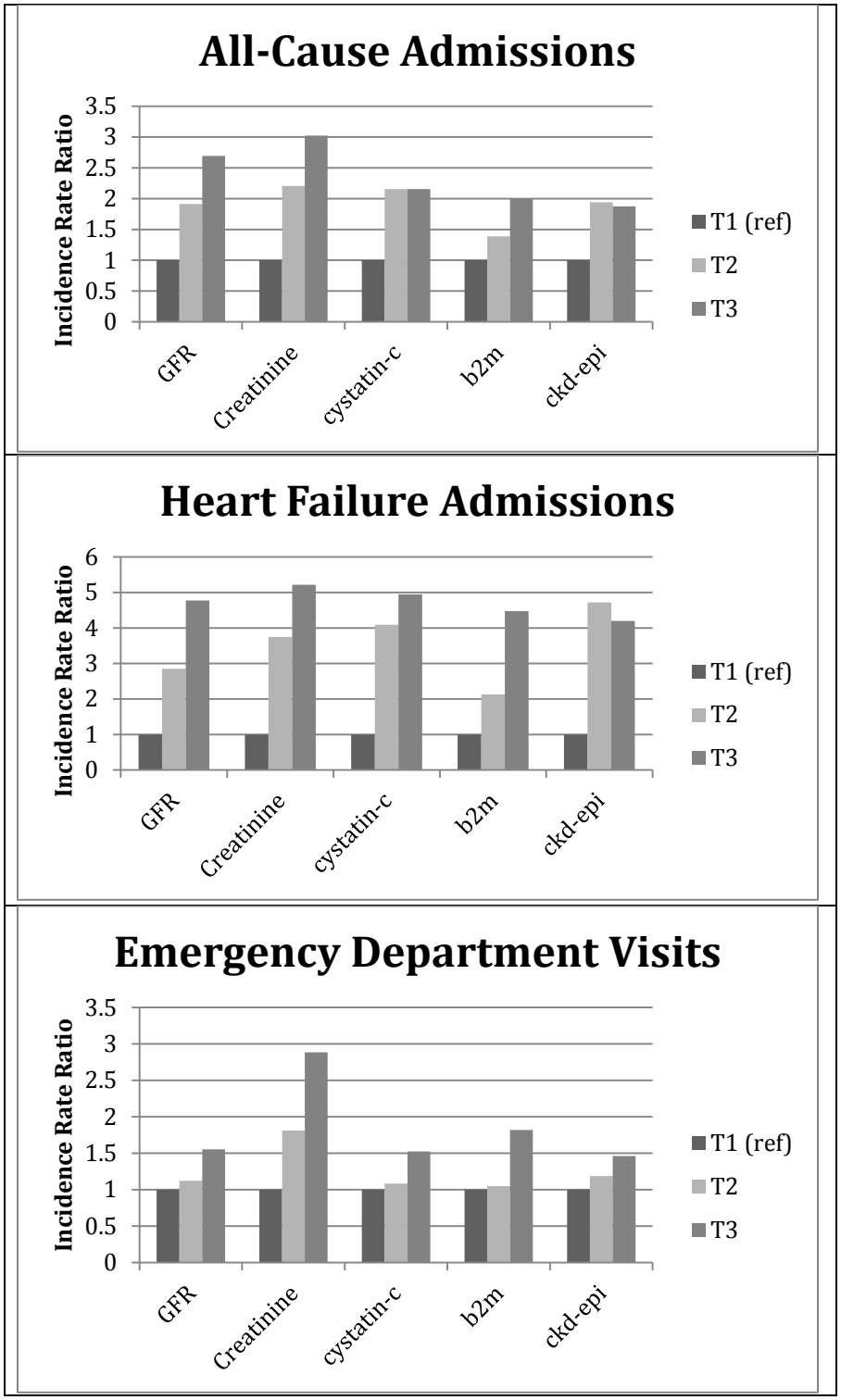
Continuous variables are expressed as mean ± SD or median (25th, 75th percentile);

ACE: angiotensin-converting enzyme inhibitor, NYHA: New York Heart Association

Table 2. Hazard of Death, LVAD, Transplantation

	Unadjusted Estimate			**Adjusted for Age, Gender, Race, CAD, LVEF, Na, SBP, therapy (ACE/ARB, beta blocker), NYHA**			
	Hazard Ratio	95% Confidence Interval	P-value	Hazard Ratio	95% Confidence Interval	P-value	C Index
Beta-2 Microglobulin	1.00		Ref	1.00		Ref	0.77
Level 2 vs. 1	2.08	0.81-5.37	0.13	2.40	0.85-6.74	0.10	
Level 3 vs. 1	2.63	1.07-6.46	0.03	2.00	0.75-5.32	0.17	
Creatinine	1.00		Ref	1.00		Ref	0.79
Level 2 vs. 1	5.04	1.13-22.54	0.03	4.33	0.94-19.91	0.06	
Level 3 vs. 1	12.84	2.99-55.15	0.00	7.30	1.58-33.70	0.01	
Cystatin C	1.00			1.00		Ref	0.78
Level 2 vs. 1	3.92	1.29-11.90	0.02	3.19	0.97-10.45	0.06	
Level 3 vs. 1	5.06	1.68-15.25	0.00	2.92	0.88-9.70	0.08	
GFR (MDRD)	1.00		Ref	1.00		Ref	0.78
Level 2 vs. 1	2.17	0.74-6.35	0.16	1.72	0.55-5.40	0.36	
Level 3 vs. 1	4.98	1.85-13.43	0.00	3.98	1.36-11.62	0.01	
GFR (CKD-Epi cystatin)	1.00		Ref	1.00		Ref	0.77
Level 2 vs. 1	3.40	1.21-9.55	0.02	2.81	0.93-8.46	0.07	
Level 3 vs. 1	3.92	1.42-10.78	0.01	2.12	0.70-6.48	0.19	

Figure 1. Healthcare Utilization



Chapter 3

Future Directions

In summary, serum creatinine is strongly associated with death, LVAD implantation and heart transplant. This association remains after controlling for relevant clinical, laboratory, and demographic confounders. Baseline serum creatinine is more strongly associated with mortality than the newer markers of renal function, beta-2 microglobulin and cystatin C. Additionally, baseline serum creatinine is strongly correlated with healthcare utilization, and may be a more useful predictor of hospitalization and emergency department use than other measures of renal function.

The burden of heart failure in the United States is immense, and it is one of the most frequent causes of hospitalizations in older Americans. These hospitalizations account for $34.4 billion in health care costs annually (10). While it has long been known that coexisting heart failure and renal dysfunction portends a poor prognosis, there is still no accepted method of quantifying risk of mortality and healthcare utilization in stable patients. This study was not powered to develop a risk prediction tool for heart failure, but does suggest that creatinine, a traditional marker of renal function that is widely available and easily measured may provide the most prognostic information of the renal biomarkers tested.

Future directions for this research would involve examining these correlations between serum creatinine and outcomes in a larger, national cohort of heart failure patients. The development of a risk model in patients with stable heart failure could aid clinicians in

determining the frequency and intensity of follow up, targeting higher risk patients. A risk prediction tool would also be helpful in future research, as studies could be targeted to patients based on their heart failure mortality risk.

In order to develop a model that is predictive of healthcare utilization, social factors such as insurance status and education as well as family structure would likely provide additional information. It is my hope to pursue these avenues of research moving forward.

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