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ORIGINAL RESEARCH

Association of Cardiac Biomarkers With the Kansas City Cardiomyopathy Questionnaire in Patients With Chronic Kidney Disease Without Heart Failure

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BACKGROUND: The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a measure of heart failure (HF) health status. Worse KCCQ scores are common in patients with chronic kidney disease (CKD), even without diagnosed heart failure (HF). Elevations in the cardiac biomarkers GDF-15 (growth differentiation factor-15), galectin-3, sST2 (soluble suppression of tumorigenesis-2), hsTnT (high-sensitivity troponin T), and NT-proBNP (N-terminal pro-B-type natriuretic peptide) likely reflect subclinical HF in CKD. Whether cardiac biomarkers are associated with low KCCQ scores is not known.

METHODS AND RESULTS: We studied participants with CKD without HF in the multicenter prospective CRIC (Chronic Renal Insufficiency Cohort) Study. Outcomes included (1) low KCCQ score <75 at year 1 and (2) incident decline in KCCQ score to <75. We used multivariable logistic regression and Cox regression models to evaluate the associations between baseline cardiac biomarkers and cross-sectional and longitudinal KCCQ scores. Among 2873 participants, GDF-15 (adjusted odds ratio 1.42 per SD; 99% CI, 1.19–1.68) and galectin-3 (1.28; 1.12–1.48) were significantly associated with KCCQ scores <75, whereas sST2, hsTnT, and NT-proBNP were not significantly associated with KCCQ scores <75 after multivariable adjustment. Of the 2132 participants with KCCQ ≥75 at year 1, GDF-15 (adjusted hazard ratio, 1.36 per SD; 99% CI, 1.12–1.65), hsTnT (1.20; 1.01–1.44), and NT-proBNP (1.30; 1.08–1.56) were associated with incident decline in KCCQ to <75 after multivariable adjustment, whereas galectin-3 and sST2 did not have significant associations with KCCQ decline.

CONCLUSIONS: Among participants with CKD without clinical HF, GDF-15, galectin-3, NT-proBNP, and hsTnT were associated with low KCCQ either at baseline or during follow-up. Our findings show that elevations in cardiac biomarkers reflect early symptomatic changes in HF health status in CKD patients.

Key Words: cardiac biomarkers ■ heart failure ■ quality of life

Patients with chronic kidney disease (CKD) are at high risk of developing heart failure (HF).[1] Cardiac biomarkers and HF health status scores are subclinical and early clinical markers of HF in CKD and other populations.[2,3] The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a health status score used in prevalent HF patients, and lower scores are associated with an increased risk of HF hospitalizations and mortality.[4] The KCCQ is an accepted clinical trial outcome as a surrogate marker of HF outcomes and can

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CLINICAL PERSPECTIVE

What Is New?

- Our study found that cardiac biomarkers GDF-15 (growth differentiation factor-15), galectin-3, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and hsTnT (high-sensitivity troponin T) were associated with health status consistent with early heart failure, as measured by the Kansas City Cardiomyopathy Questionnaire, among participants with chronic kidney disease without baseline heart failure.

What Are The Clinical Implications?

- Elevations in cardiac biomarkers may reflect early symptoms of heart failure in patients with chronic kidney disease.

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
aOR	adjusted odds ratio
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRIC	Chronic Renal Insufficiency Cohort
ESKD	end-stage kidney disease
GDF-15	growth differentiation factor-15
HF	heart failure
hsTnT	high-sensitivity troponin T
KCCQ	Kansas City Cardiomyopathy Questionnaire
NT-proBNP	N-terminal pro-B-type natriuretic peptide
sST2	soluble suppression of tumorigenesis-2

also be used to track longitudinal health status.[5] In our previous work, we reported that CKD patients without diagnosed HF had a high prevalence of low KCCQ scores and that lower KCCQ scores were associated with *incident* HF.[6,7] However, the relationships between cardiac biomarkers and heart failure health status, as measured by the KCCQ, have not been studied to our knowledge.

In studies of persons with and without CKD, elevations in cardiac biomarkers GDF-15 (growth differentiation factor-15), galectin-3, sST2 (soluble suppression of tumorigenesis-2), hsTnT (high-sensitivity troponin T), and NT-proBNP (N-terminal pro-B-type natriuretic peptide) have been associated with an increased risk of incident HF.[2,3,8–11] GDF-15 is a stress-related cytokine upregulated in cardiac ischemia/reperfusion injury.[12] Galectin-3 is a protein involved with broad cellular functions including cell-cell adhesion and cell-matrix interactions and is involved in HF pathogenesis via fibrosis and inflammation.[13] sST2, a member of the interleukin-1 receptor family, binds to the cardioprotective cytokine interleukin-33 in settings of cardiac stress, contributing to cardiac injury.[14] hsTnT is a component of cardiac myocytes and specific marker of cardiac ischemia, and NT-proBNP is released in response to myocardial stretch.[15,16] Understanding the associations of cardiac biomarkers with patient health status related to HF may improve early detection and diagnosis of HF in CKD patients and could offer pathophysiological insights into HF development in CKD.

To understand the relationships between cardiac biomarkers and health status consistent with early HF, we evaluated the association of GDF-15, galectin-3, sST-2, hsTnT, and NT-proBNP with KCCQ health status scores at baseline as well as longitudinally. We hypothesized that cardiac biomarkers would be associated with low (worse) KCCQ scores at baseline and with worsening KCCQ scores over a 4-year period.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the CRIC (Chronic Renal Insufficiency Cohort) Study at www.cristudy.org.

Study Design and Population

We performed cross-sectional and longitudinal analyses to evaluate associations of cardiac biomarkers with HF health status among persons with CKD in the CRIC Study. The CRIC Study is a prospective multicenter longitudinal cohort study that included 3939 adult patients with mild to moderate CKD, with an estimated glomerular filtration rate of 20 to 70 mL/min.[17] Patients were recruited at 7 clinical centers (with 13 enrolling sites) across the United States from May 2003 to March 2007. Exclusion criteria were presence of New York Heart Association class III or IV HF, cirrhosis, HIV, pregnancy, previous receipt of dialysis, history of transplant, polycystic kidney disease, and others as previously described.[18] All study participants provided written informed consent, and the study protocol was approved by institutional review boards at each of the participating sites.

For the present analysis, we excluded CRIC participants who did not have all 5 cardiac biomarkers measured at baseline (N=277); were missing a KCCQ score at year 1 (N=410) which was the earliest measure of

the KCCQ in CRIC; or had end-stage kidney disease (ESKD) at year 1 (N=40). We further excluded patients with HF or missing HF status at year 1 (N=339) as our objective was to evaluate CKD participants without diagnosed HF. Of the 3939 participants in the original CRIC study population, 2873 participants were included in the analytic population for our cross-sectional analysis.

Predictors

The primary predictors were levels of the cardiac biomarkers GDF-15, galectin-3, sST-2, hsTnT, and NT-proBNP measured at baseline. GDF-15, galectin-3, and sST2 were measured from EDTA plasma stored at 70°C from samples at baseline in batch at the University of Pennsylvania Laboratory in 2017. GDF-15, galectin-3, and sST2 were measured using ELISA (R&D Systems) and had intra-assay coefficients of variation of 2.0%, 4.0%, and 2.6%, respectively. All assays were measured in duplicate.

The biomarkers hsTnT and NT-proBNP were measured at baseline in 2008 from EDTA plasma stored at –70°C using a chemiluminescent microparticle immunoassay (www.roche-diagnostics.us) on the ElecSys 2010 at the University of Maryland. HsTnT was measured using the highly sensitive assay with a range of values from 3 to 10 000 ng/L. Any values below the lower limit of blank were characterized as "undetectable." The coefficient of variation was 6.0% at a level of 26 ng/L and 5.4% at 2140 ng/L. The value at the 99th percentile cutoff from a healthy reference population was 13 ng/L for hsTnT with a 10% coefficient of variation. The range of values for NT-proBNP, was from 5 to 35 000 pg/mL and the coefficient of variation was 9.3% at a level of 126 pg/mL and 5.5% at 4319 pg/mL.

Outcomes

The primary outcomes were baseline KCCQ Overall Summary Scores and an incident decline in KCCQ Overall Summary Scores. The KCCQ Overall Summary Score includes the total symptom, physical function, social limitations and quality of life scores, and ranges from 0 to 100, with lower scores reflecting worse health status. For the present study, initial KCCQ scores were measured at year 1. We dichotomized the score at 75 to indicate health status consistent with early HF, which was considered a meaningful threshold of health status consistent with HF based on prior studies and our work in the CRIC Study.[4,6,19] The KCCQ is a 23-item self-administered questionnaire measuring participants' perception of their health status, completed by participants at annual CRIC study visits.[4] It is a validated survey instrument that is highly sensitive for monitoring changes in HF health status.[5,20,21] The KCCQ incorporates questions related to respiratory symptoms, activities of daily living, extremity swelling, fatigue, and lifestyle. It consists of 6 domains: symptoms, physical function, quality of life, social limitation, self-efficacy, and symptom stability.

As an additional outcome, we examined the development of incident decline in KCCQ scores using annual measures of KCCQ ascertained at CRIC Study visits from years 1 to 5. This analysis was restricted to the 2132 CRIC participants included in our study who had KCCQ ≥75 at year 1. We defined incident decline as a change in KCCQ meeting 2 criteria: (1) crossing the threshold of a KCCQ score of 75 by transitioning from KCCQ≥75 to a KCCQ<75, and (2) a mean of >3 points per year decrease over the participant's follow-up time, equivalent to a >12 point decline in KCCQ score from year 1 to year 5. We defined this threshold for a clinically significant change based on clinical trial data in other populations that have evaluated the trajectory of KCCQ over time.[22–25]

Covariates

Covariates were measured at year 1 and included participant demographics, comorbidities, clinical variables, laboratory variables, and medications known to be associated with cardiac biomarkers and health status. At the baseline study visit, participants provided information on their demographic characteristics, including age, sex, and race/ethnicity.[17] Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other. At the baseline study visit and each subsequent study visit, participants reported their comorbidities including cardiovascular disease, myocardial infarction/revascularization, chronic obstructive pulmonary disease, atrial fibrillation, and stroke. Diabetes mellitus was defined as a fasting glucose >126 mg/dL, a nonfasting glucose >200 mg/dL, or use of insulin or other antidiabetic medication. Blood pressure and anthropometric measurements were assessed using standard protocols.[26] Body mass index was calculated as weight in kilograms divided by height in meters squared. Serum creatinine was measured using an enzymatic method on an Ortho Vitros 950 at the CRIC Central Laboratory and standardized to isotope dilution mass spectrometry-traceable values.[27] Estimated glomerular filtration rate was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation.[28] Additional assays measured 24-hour urine total protein, which was measured at the CRIC Study Central Laboratory. Participants reported their medication usage at baseline and subsequent study visits, including use of angiotensin-converting enzyme

inhibitors or angiotensin receptor blockers, diuretics, and beta blockers.[17] Transthoracic echocardiograms were performed at 1 year and provided data on left ventricular ejection fraction and left ventricular mass index as previously described.[29] Assessments were performed using 2-dimensional images and a standard imaging protocol according to American Society of Echocardiography guidelines and quantified centrally by a highly trained Registered Diagnostic Cardiac Sonographer.[30] Our analyses were adjusted using covariates at year 1 time points.

Statistical Analysis

We first described baseline characteristics of the overall study population. Levels of GDF-15, galectin-3, sST-2, and NT-proBNP were divided into quintiles (because there are no clinically meaningful or prespecified cutoffs in patients with CKD). Because of the large number of participants with undetectable hsTntT, we categorized hsTnT as undetectable (<10 ng/L) and in tertiles across the detectable range, similar to our prior published work.[31,32] Characteristics of the study population by biomarker category were reported as mean and SD or median and interquartile range for continuous variables and as number and percentage for categorical variables. Proportions of participants with KCCQ scores <75 were reported across biomarker categories.

In cross-sectional analyses, separate multivariable logistic regression models were used to evaluate the associations between each cardiac biomarker and KCCQ scores <75. Cardiac biomarkers were modeled as both continuous variables (per SD increase) and in categories. We performed a series of nested models that were specified prior to conducting the analyses. Model 1 was adjusted for age, sex, and race/ethnicity. Model 2 was additionally adjusted for biologically relevant covariates: cardiovascular disease, myocardial infarction/revascularization, chronic obstructive pulmonary disease, atrial fibrillation, stroke, diabetes mellitus, systolic blood pressure, body mass index, current smoking, estimated glomerular filtration rate, 24-hour urinary protein, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, diuretic use, and beta blocker use.

Using Cox regression, we then examined the association of baseline biomarker levels with incident decline in KCCQ scores among participants with year 1 KCCQ ≥75, which we defined as a decrease in KCCQ scores to <75 and a mean of >3 points per year decrease over the participant's follow-up time. This analysis was limited to 2132 participants who had KCCQ ≥75 at year 1. Participants were censored at year 5, loss to follow-up, withdrawal, death, development of ESKD, or development of incident HF. We censored participants at the development of ESKD for several reasons. First, the risk of subclinical HF is likely different in patients with ESKD compared with CKD. Further, the KCCQ has not been validated for use in the ESKD population. We chose to censor participants who developed incident HF, as we sought to evaluate the association of cardiac biomarkers with health status consistent with early HF before the development of HF. Models were adjusted for the same covariates as in the cross-sectional analysis listed previously. We evaluated the proportional hazards assumption and found no violations for any biomarker in continuous unadjusted models (GDF-15: P=0.66; galectin-3: P=0.48; sST-2: P=0.90; hsTNT: P=0.24; NT-proBNP: P=0.90).

We performed several sensitivity analyses to evaluate the robustness of our results. We first included all 5 biomarkers in the multivariable model to evaluate if the associations with biomarkers and KCCQ scores were independent of the other biomarkers (Model 3). We also adjusted the model for left ventricular (LV) mass and ejection fraction to determine if the observed associations were independent of other established subclinical HF measures (Model 4). For the longitudinal analyses, we added adjustment for baseline KCCQ scores to evaluate the decline in KCCQ scores independent of the baseline value (Model 5). In another sensitivity analysis, we evaluated a more restrictive definition of KCCQ decline, defined as developing a KCCQ <60 and having an average decline in KCCQ score of >5 points/year among participants with a baseline KCCQ≥60.

All analyses were performed using the R 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) software environment. We accounted for multiple comparisons using a Bonferroni correction, where a 2-sided P value of 0.01 was considered statistically significant for all analyses.

RESULTS

Characteristics of the Study Population

Among the 2873 participants included in the cross-sectional analysis, mean age was 59 years and estimated glomerular filtration rate was 43 mL/min per 1.73 m^2. Participants had a high prevalence of comorbidities, including diabetes mellitus (47%) and cardiovascular disease (28%), and the majority were prescribed angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or diuretic medications (Table 1). The median and interquartile range for each biomarker were as follows: GDF-15 median 1377, interquartile range (949–2016) pg/mL; galectin-3 13.7

Table 1. Demographic Characteristics by Quintile of Growth Differentiation Factor-15 (N=2873)

	Overall (N=2873)	Quintile 1 ≤856 pg/mL (N=579)	Quintile 2 857 to 1200 pg/mL (N=570)	Quintile 3 1201 to 1570 pg/mL (N=575)	Quintile 4 1571 to 2220 pg/mL (N=574)	Quintile 5 >2220 pg/mL (N=575)
Demographics						
Age	59 (10.8)	53 (11.3)	58 (11.0)	60 (10.5)	62 (9.2)	62 (9.0)
Male	1558 (54)	287 (50)	304 (53)	315 (55)	313 (55)	339 (59)
Race/ethnicity						
Non-Hispanic white	1314 (46)	334 (58)	266 (47)	277 (48)	237 (41)	200 (35)
Non-Hispanic black	1111 (39)	192 (33)	222 (39)	209 (36)	242 (42)	246 (43)
Hispanic	324 (11)	30 (5)	48 (8)	72 (13)	69 (12)	105 (18)
Other	124 (4)	23 (4)	34 (6)	17 (3)	26 (5)	24 (4)
Comorbidities						
Cardiovascular disease	806 (28)	68 (12)	120 (21)	175 (30)	218 (38)	225 (39)
Myocardial infarction/prior revascularization	530 (18)	47 (8)	82 (14)	108 (19)	143 (25)	150 (26)
Chronic obstructive pulmonary disease	121 (4)	14 (2)	22 (4)	30 (5)	23 (4)	32 (6)
Atrial fibrillation	419 (15)	70 (12)	65 (11)	84 (15)	94 (16)	106 (18)
Stroke	269 (9)	19 (3)	39 (7)	59 (10)	78 (14)	74 (13)
Diabetes mellitus	1341 (47)	100 (17)	207 (36)	295 (51)	338 (59)	401 (70)
Clinical variables						
Systolic blood pressure, mm Hg	126.4 (21.3)	118.5 (18.2)	123.5 (19.5)	125.8 (19.8)	130.8 (21.9)	133.8 (23.4)
Body mass index, kg/m^2	32 (7.6)	31 (7.2)	32 (7.5)	33 (7.6)	32 (7.7)	32 (7.8)
Current smoking	340 (12)	26 (4)	45 (8)	67 (12)	94 (16)	108 (19)
Laboratory variables						
Estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration), mL/min per 1.73 m^2	43.2 (15.7)	58.1 (13.3)	46.4 (12.2)	41.1 (12.5)	37.3 (13.2)	32.6 (13.8)
Urinary protein to creatinine ratio from 24 h urine test	117 (52–602)	60 (39–107)	92 (48–332)	123 (54–530)	178 (62–905)	448 (121–1958)
Ejection fraction, %	55.3 (7.3)	55.2 (7.1)	55.8 (7.1)	55.4 (7.1)	55.3 (7.4)	54.5 (7.7)
Left ventricular mass index, g	62.8 (22.3)	54.6 (20.1)	59.7 (19.8)	63.2 (20.7)	66.5 (22.2)	71.9 (24.9)
Medications						
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	1972 (69)	314 (54)	411 (72)	427 (74)	423 (74)	397 (69)
Diuretics	1616 (56)	204 (35)	290 (51)	353 (61)	373 (65)	396 (69)
Beta blockers	1349 (47)	173 (30)	259 (45)	276 (48)	315 (55)	326 (57)

Entries are mean (SD) for continuous covariates or N (%) for categorical covariates, except as noted.

(9.9–18.7) pg/mL; sST-2 15.1 (11.2–20.2) pg/mL; hsTnT 13.2 (8.1–22.4) ng/L; and NT-proBNP 109 (41–285) pg/mL. Participants with higher levels of GDF-15 were older; more likely to be male, black, or Hispanic; and had a higher prevalence of comorbidities. Participants with higher GDF-15 were more likely to use angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, and beta blockers (Table 1). Similar patterns were seen across the other biomarkers (Tables S1-S4).

Cross-sectional Associations of Cardiac Biomarkers with KCCQ Scores

Higher quintiles of GDF-15, galectin-3, and sST-2 had higher proportions of KCCQ scores <75 and were incrementally associated with KCCQ scores of <75 in unadjusted analyses (Figure and Table 2). When adjusting for patient demographics and biologically relevant covariates, GDF-15 (adjusted odds ratio [aOR] 1.42 per SD higher GDF-15; 99% CI, 1.19–1.68) was significantly associated with KCCQ scores of <75, and the highest quintile of GDF-15 compared with the lowest quintile was associated with an approximately 2-fold odds of KCCQ <75 (Table 2). Galectin-3 was also significantly associated with KCCQ scores <75 when modeled continuously (aOR 1.28 per SD higher galectin-3; 99% CI, 1.12–1.48), and the highest quintile was also associated with an approximately 2-fold odds of KCCQ <75 when compared with the lowest quintile (Table 2). In continuous analyses, sST-2 was significantly associated with KCCQ scores <75 (aOR 1.20 per SD higher sST2; 99% CI, 1.05–1.38) when adjusted for participant demographics, but this association did not reach statistical significance after adjustment for biologically relevant covariates (Table 2).

The clinically available biomarkers hsTnT and NT-proBNP were significantly associated with year 1 KCCQ scores of <75 in unadjusted analyses (Table 2). These associations did not attenuate when adjusting for age, sex, and race/ethnicity. In the continuous model adjusted for comorbidities and clinical variables, the association of hsTnT with KCCQ scores was not statistically significant (aOR 1.10 per SD higher hsTnT; 99% CI, 0.93–1.30). Similarly, NT-proBNP was not associated with KCCQ scores in the adjusted model (aOR 1.03 per SD higher NT-proBNP; 99% CI, 0.88–1.21). In categorical analyses, neither hsTnT nor NT-proBNP was significantly associated with cross-sectional KCCQ scores in adjusted analyses.

Cardiac Biomarkers and Incident Decline in KCCQ

Of the 2132 participants with year 1 KCCQ ≥75, 362 declined to KCCQ <75 with a >3 point per year average decline. Persons with incident decline in KCCQ were more likely to be black or Hispanic and had a higher prevalence of cardiovascular disease and diabetes mellitus, compared with those without incident decline (Table 3). GDF-15, galectin-3, NT-proBNP, and

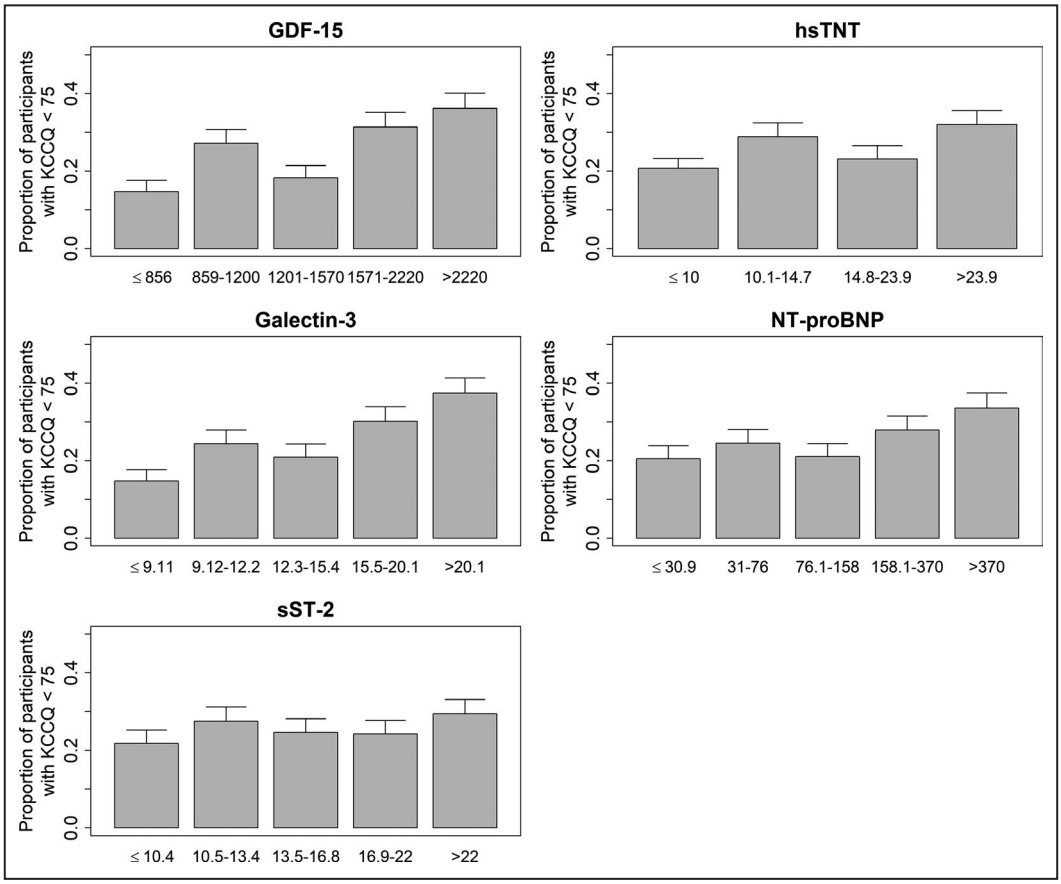

Figure. Proportion of participants with year 1 KCCQ<75 by biomarker category (N=2873).
KCCQ indicates Kansas City Cardiomyopathy Questionnaire.

Table 2. Cross-Sectional Association of Cardiac Biomarkers With Year 1 KCCQ Score <75 in Persons With CKD Without HF in the CRIC Study (N=2873)

	KCCQ score <75 Model 0 OR (99% CI)	KCCQ score <75 Model 1 aOR (99% CI)	KCCQ Score <75 Model 2 aOR (99% CI)
GDF-15 continuous model			
Log(GDF-15) per 1 SD (0.58 pg/mL) increase	1.56 (1.39, 1.75)*	1.60 (1.41, 1.82)*	1.42 (1.19, 1.68)*
GDF-15 categorical model			
Quintile 1 (≤856 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (857–1200 pg/mL)	1.30 (0.86, 1.96)	1.31 (0.86, 2.01)	1.08 (0.67, 1.73)
Quintile 3 (1201–1570 pg/mL)	2.16 (1.47, 3.19)*	2.31 (1.54, 3.47)*	1.65 (1.03, 2.66)*
Quintile 4 (1571–2220 pg/mL)	2.66 (1.81, 3.89)*	2.81 (1.87, 4.23)*	1.93 (1.17, 3.18)*
Quintile 5 (>2220 pg/mL)	3.29 (2.26, 4.80)*	3.52 (2.34, 5.29)*	2.35 (1.39, 3.97)*
Galectin-3 continuous model			
Log(Galectin-3) per 1 SD (0.50 pg/mL) increase	1.61 (1.42, 1.83)*	1.49 (1.31, 1.69)*	1.28 (1.12, 1.48)*
Galectin-3 categorical model			
Quintile 1 (≤9.11 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (9.12–12.2 pg/mL)	1.53 (1.02, 2.29)*	1.45 (0.96, 2.18)	1.29 (0.84, 1.99)
Quintile 3 (12.3–15.4 pg/mL)	1.86 (1.26, 2.75)*	1.64 (1.10, 2.45)*	1.36 (0.88, 2.08)
Quintile 4 (15.5–20.1 pg/mL)	2.49 (1.70, 3.65)*	2.15 (1.46, 3.19)*	1.63 (1.06, 2.50)*
Quintile 5 (>20.1 pg/mL)	3.45 (2.37, 5.02)*	2.76 (1.87, 4.07)*	1.80 (1.17, 2.78)*
sST-2 continuous model			
Log(sST-2) per 1 SD (0.55 pg/mL) increase	1.12 (0.99, 1.26)	1.20 (1.05, 1.38)*	1.12 (0.98, 1.28)
sST-2 categorical model			
Quintile 1 (≤10.4 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (10.5–13.4 pg/mL)	1.17 (0.81, 1.67)	1.25 (0.86, 1.80)	1.09 (0.73, 1.64)
Quintile 3 (13.5–16.8 pg/mL)	1.36 (0.95, 1.94)	1.51 (1.05, 2.17)*	1.35 (0.91, 2.01)
Quintile 4 (16.9–22 pg/mL)	1.14 (0.80, 1.64)	1.37 (0.94, 2.00)	1.06 (0.70, 1.60)
Quintile 5 (> 22 pg/mL)	1.49 (1.05, 2.12)*	1.90 (1.31, 2.75)*	1.51 (1.00, 2.28)*
hsTnT continuous model			
Log(hsTnT) per 1 SD (0.77 ng/L) increase	1.30 (1.17, 1.45)*	1.44 (1.26, 1.63)*	1.10 (0.93, 1.31)
hsTnT categorical model			
<Lower limit of detection (<10 ng/L)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Tertile 1 (10.1–14.7 ng/L)	1.15 (0.83, 1.59)	1.33 (0.95, 1.87)	1.06 (0.73, 1.55)
Tertile 2 (14.8–23.9 ng/L)	1.55 (1.15, 2.10)*	1.91 (1.37, 2.65)*	1.20 (0.82, 1.75)
Tertile 3 (>23.9 ng/L)	1.80 (1.34, 2.42)*	2.26 (1.61, 3.16)*	1.17 (0.77, 1.78)
NT-proBNP continuous model			
Log(NT-proBNP) per 1 SD (1.60 pg/mL) increase	1.29 (1.15, 1.46)*	1.30 (1.14, 1.47)*	1.03 (0.88, 1.21)
NT-proBNP categorical model			
Quintile 1 (≤30.9 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (31–76 pg/mL)	1.03 (0.71, 1.50)	1.00 (0.68, 1.46)	0.86 (0.57, 1.30)
Quintile 3 (76.1–158 pg/mL)	1.26 (0.87, 1.81)	1.26 (0.87, 1.84)	0.95 (0.63, 1.44)
Quintile 4 (158.1–370 pg/mL)	1.50 (1.05, 2.14)*	1.50 (1.03, 2.17)*	0.95 (0.61, 1.47)
Quintile 5 (>370 pg/mL)	1.96 (1.38, 2.78)*	1.92 (1.32, 2.79)*	1.03 (0.65, 1.63)

Model 0: Unadjusted; Model 1: Age, sex, race/ethnicity; Model 2: M1 + myocardial infarction, chronic obstructive pulmonary disease, atrial fibrillation, stroke, diabetes mellitus, systolic blood pressure, body mass index, current smoking, estimated glomerular filtration rate, 24 h urinary protein, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, diuretics, and beta blocker use; aOR indicates, adjusted odds ratio; CKD, chronic kidney disease; CRIC, Chronic Renal Insufficiency Cohort; GDF-15, growth differentiation factor-15; HF, heart failure; hsTnT, high-sensitivity troponin T; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; and sST-2, soluble suppression of tumorigenesis-2.

*$P<0.01$.

hsTnT were associated with incident decline in KCCQ scores between years 1 and 5 when modeled continuously and adjusted for age, sex, and race/ethnicity (Table 4). The association of sST-2 and incident decline in KCCQ scores did not reach statistical significance in unadjusted analyses and in analyses adjusted

Table 3. Characteristics of Participants Who Had Incident Decline in KCCQ Scores*, as Defined by KCCQ <75 and An Average Decline in KCCQ Score of >3 Points/Year (N=2132)

	Incident Decline in KCCQ*(N=362)	No Incident Decline in KCCQ(N=1770)
Demographics		
Age	61.3 (10.2)	58.4 (11.3)
Male	182 (50)	1049 (59)
Race/ethnicity		
Non-Hispanic white	143 (40)	931 (53)
Non-Hispanic black	150 (41)	585 (33)
Hispanic	55 (15)	170 (10)
Other	14 (4)	84 (5)
Comorbidities		
Cardiovascular disease	127 (35)	372 (21)
Myocardial infarction/prior revascularization	86 (24)	254 (14)
Chronic obstructive pulmonary disease	16 (4)	38 (2)
Atrial fibrillation	57 (16)	208 (12)
Stroke	51 (14)	108 (6)
Diabetes mellitus	185 (51)	707 (40)
Clinical variables		
Systolic blood pressure, mm Hg	128.6 (20.9)	124.4 (20.5)
Body mass index, kg/m^2	32.4 (7.2)	30.2 (6.4)
Current smoking	47 (13)	158 (9)
Laboratory variables		
Estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration), mL/min per 1.73 m^2	41.4 (13.5)	44.7 (15.6)
Urinary protein to creatinine ratio from 24 h urine test	149.9 (58.0–635.7)	99.9 (48.7–498.0)
Ejection fraction, %	54.7 (7.2)	55.4 (7.3)
Left ventricular mass index, g	65.0 (21.1)	59.3 (21.0)
Medications		
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	249 (69)	1217 (69)
Diuretics	219 (60)	889 (50)
Beta blockers	177 (49)	749 (42)

Entries are mean (SD) for continuous covariates or N (%) for categorical covariates, except as noted.

KCCQ indicates Kansas City Cardiomyopathy Questionnaire.

*Incident decline in KCCQ defined as participants with KCCQ≥75 developing a KCCQ <75 and having an average decline in KCCQ score of >3 points/y.

for participant demographics. There were 163 ESKD events (incidence rate 26.1 per 100 person-years; 95% CI, 23.4–28.8) and 80 incident HF events (incidence rate 3.5 per 100 person-years; 95% CI, 3.0–3.9), which were censoring events in the longitudinal analyses.

When adjusted for comorbidities and clinical variables in Model 2, GDF-15 (adjusted hazard ratio [aHR] 1.36 per SD higher GDF-15; 99% CI, 1.12–1.65), hsTnT (aHR 1.20 per SD higher hsTnT; 99% CI, 1.01–1.44), and NT-proBNP (aHR 1.30 per SD higher NT-proBNP; 99% CI, 1.08–1.56) were significantly associated with incident decline in KCCQ scores. The highest quintile of GDF-15 was associated with a greater than 3-fold risk of incident decline in KCCQ scores, the largest association among the 5 biomarkers.

Sensitivity Analyses

When adjusting for all 5 biomarkers in our multivariable model (correlation matrix in Table S5), GDF-15 and galectin-3 were associated with KCCQ scores <75 in cross-sectional analyses. In longitudinal analyses, GDF-15 and NT-proBNP were associated with incident KCCQ <75; however, the association of hsTnT was no longer statistically associated with a decline in KCCQ scores after adjustment for the other biomarkers (Model 3, Table S6). Additional adjustment for left ventricular mass and left ventricular ejection fraction did not meaningfully attenuate the associations between the cardiac biomarkers of interest and KCCQ scores <75 at baseline or incident decline in KCCQ scores (Model 4, Table S6). The additional adjustment for baseline KCCQ scores also did not meaningfully change the results of longitudinal analyses (Model 5, Table S6).

The cardiac biomarkers GDF-15 and hsTnT were associated with incident decline to KCCQ <60 and having an average decline in KCCQ score of >5 points/year, among participants with a baseline KCCQ≥60, similar to the primary analysis (Table S7). Although NT-proBNP was associated with KCCQ decline to <75, the association of NT-proBNP and KCCQ decline to <60 did not reach statistical significance.

DISCUSSION

Previous work has shown that persons living with CKD without diagnosed HF have low KCCQ scores, suggestive of health status consistent with early HF.[6,23–25] In this large, longitudinal study of CKD patients we found significant cross-sectional associations of newer cardiac measures GDF-15 and galectin-3 with health status consistent with early HF, whereas sST2, NT-proBNP, and hsTnT were not associated with baseline KCCQ scores <75 in models adjusted for numerous potential confounders. In longitudinal analyses, GDF-15 had the strongest association with incident decline in KCCQ scores, followed by NT-proBNP and hsTnT, whereas the associations of sST2 and galectin-3 with decline in KCCQ scores were not statistically significant. These findings indicate that circulating cardiac

Table 4. Association of Cardiac Biomarkers With Incident Decline in KCCQ Scores*, Among Participants With Year 1 KCCQ ≥75 (N=2132)

	Incident Decline in KCCQ* Model 0 HR (99% CI)	Incident Decline in KCCQ Model 1 aHR (99% CI)	Incident Decline in KCCQ Model 2 aHR (99% CI)
GDF-15 continuous model			
Log(GDF-15) per 1 SD (0.58 pg/mL) increase	1.67 (1.45, 1.92)†	1.57 (1.35, 1.83)†	1.36 (1.12, 1.65)†
GDF-15 categorical model			
Quintile 1 (≤856 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (857–1200 pg/mL)	2.06 (1.23, 3.44)†	1.89 (1.12, 3.20)†	1.63 (0.94, 2.83)
Quintile 3 (1201–1570 pg/mL)	2.33 (1.39, 3.90)†	2.08 (1.23, 3.53)†	1.59 (0.89, 2.83)
Quintile 4 (1571–2220 pg/mL)	3.77 (2.30, 6.18)†	3.28 (1.94, 5.53)†	2.34 (1.27, 4.30)†
Quintile 5 (>2220 pg/mL)	5.28 (3.23, 8.63)†	4.55 (2.70, 7.68)†	3.15 (1.68, 5.89)†
Galectin-3 continuous model			
Log(Galectin-3) per 1 SD (0.50 pg/mL) increase	1.36 (1.17, 1.58)†	1.22 (1.05, 1.42)†	1.08 (0.92, 1.26)
Galectin-3 categorical model			
Quintile 1 (≤9.11 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (9.12–12.2 pg/mL)	1.53 (0.96, 2.45)	1.42 (0.89, 2.28)	1.33 (0.83, 2.15)
Quintile 3 (12.3–15.4 pg/mL)	1.84 (1.16, 2.91)†	1.61 (1.02, 2.56)†	1.43 (0.90, 2.28)
Quintile 4 (15.5–20.1 pg/mL)	2.26 (1.44, 3.55)†	1.84 (1.17, 2.91)†	1.46 (0.91, 2.33)
Quintile 5 (>20.1 pg/mL)	2.79 (1.76, 4.42)†	2.08 (1.29, 3.34)†	1.50 (0.92, 2.46)
sST-2 continuous model			
Log(sST-2) per 1 SD (0.55 pg/mL) increase	1.11 (0.96, 1.29)	1.16 (0.99, 1.35)	1.08 (0.92, 1.26)
sST-2 categorical model			
Quintile 1 (≤10.4 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (10.5–13.4 pg/mL)	1.13 (0.74, 1.73)	1.15 (0.75, 1.77)	1.02 (0.66, 1.58)
Quintile 3 (13.5–16.8 pg/mL)	1.00 (0.64, 1.56)	1.00 (0.64, 1.57)	0.90 (0.57, 1.41)
Quintile 4 (16.9–22 pg/mL)	1.16 (0.75, 1.78)	1.22 (0.78, 1.91)	0.97 (0.61, 1.53)
Quintile 5 (> 22 pg/mL)	1.51 (1.00, 2.29)†	1.77 (1.15, 2.73)†	1.46 (0.93, 2.28)
hsTnT continuous model			
Log(hsTnT) per 1 SD (0.78 ng/L) increase	1.42 (1.24, 1.62)†	1.44 (1.24, 1.68)†	1.20 (1.01, 1.44)†
hsTnT categorical model			
< lower limit of detection (<10 ng/L)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Tertile 1 (10.1–14.7 ng/L)	1.51 (1.03, 2.23)†	1.56 (1.05, 2.32)†	1.34 (0.89, 2.02)
Tertile 2 (14.8–23.9 ng/L)	1.81 (1.25, 2.64)†	1.86 (1.25, 2.79)†	1.40 (0.92, 2.14)
Tertile 3 (>23.9 ng/L)	2.52 (1.74, 3.65)†	2.67 (1.76, 4.04)†	1.75 (1.10, 2.80)†
NT-proBNP continuous model			
Log(NT-proBNP) per 1 SD (1.60 pg/mL) increase	1.59 (1.37, 1.85)†	1.51 (1.29, 1.76)†	1.30 (1.08, 1.56)†
NT-proBNP categorical model			
Quintile 1 (≤31.9 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (31–76 pg/mL)	1.64 (1.01, 2.67)†	1.51 (0.93, 2.46)	1.31 (0.79, 2.15)
Quintile 3 (76.1–158 pg/mL)	1.57 (0.95, 2.58)	1.42 (0.86, 2.37)	1.12 (0.66, 1.88)
Quintile 4 (158.1–370 pg/mL)	2.73 (1.72, 4.32)†	2.47 (1.54, 3.98)†	1.75 (1.05, 2.92)†
Quintile 5 (>370 pg/mL)	3.48 (2.19, 5.55)†	2.89 (1.78, 4.69)†	1.88 (1.09, 3.24)†

Model 0: Unadjusted; Model 1: Age, sex, race/ethnicity; Model 2: M1 + myocardial infarction, chronic obstructive pulmonary disease, atrial fibrillation, stroke, diabetes mellitus, systolic blood pressure, body mass index, current smoking, estimated glomerular filtration rate, 24 h urinary protein, angiotensin-converting enzyme inhibitosr/angiotensin receptor blockers, diuretics, and beta blocker use; aHR indicates adjusted hazard ratio; GDF-15, growth differentiation factor-15; HR, hazard ratio; hsTnT, high-sensitivity troponin T; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and sST-2, soluble suppression of tumorigenesis-2.

*Incident decline in KCCQ defined as participants with KCCQ≥75 developing a KCCQ<75 and having an average decline in KCCQ score of >3 points/y.

†$P<0.01$.

biomarkers signal greater risk of both low and worsening health status consistent with early HF and may provide information related to the patient experience of early HF.

Newer cardiac biomarkers may contribute to a greater burden of health status consistent with early HF in CKD patients via several pathophysiologic mechanisms. GDF-15 is upregulated in cardiac ischemia/reperfusion injury and conditions of pressure overload and cardiac hypertrophy, which commonly occur in CKD patients even in the absence of clinical HF.[12,33,34] Among the 5 biomarkers, GDF-15 had a strong association with baseline and longitudinal KCCQ scores over a 4-year period, suggesting that GDF-15, in addition to its role in HF pathogenesis, may best capture the patient experience of early HF in this population with CKD. Similarly, galectin-3′s role in fibrosis and inflammation has been implicated in the pathogenesis of HF, including cardiac fibroblast proliferation and collagen deposition.[13,35,36] These changes lead to cardiac hypertrophy and ventricular remodeling, which may explain the development of dyspnea that is measured by the KCCQ. Several factors may explain why galactin-3 was significantly associated with KCCQ <75 cross-sectionally but not longitudinally. First, the established cardiac biomarkers hsTnT and NT-proBNP may be more sensitive to longitudinal heart failure status and changes over time, whereas galactin-3 may be less cardiac specific, as it is also a marker of inflammation and fibrosis. We also find that sST2 was associated with baseline KCCQ scores in models adjusted for participant demographics, but this association did not reach statistical significance at a $P<0.01$ in models additionally adjusted for biologically relevant covariates. sST2, a member of the interleukin-1 receptor family, is upregulated in HF, myocardial stretch, and ischemia.[37] sST2 is a marker of mortality risk in patients with cardiovascular disease, but its association with quality of life has been less studied.[38] Taken together, our results suggest that the newer biomarkers GDF-15 and galectin-3 reflect physiological processes that are important to the patient experience of early HF.

The relationships between GDF-15 and galectin-3 with KCCQ scores have not been previously described; however, these cardiac biomarkers have been studied in relation to other HF quality of life instruments. An analysis in patients with HF and controls found an association between GDF-15 and the Short Form 36 physical functioning scale; however, it did not reach statistical significance after adjusting for numerous covariates ($P=0.052$).[39] In a trial of HF patients with preserved ejection fraction, baseline galectin-3 levels were significantly correlated with the Short Form 36 after multivariable adjustment.[40] However, 2 studies in HF patients showed no association between galectin-3 levels and the Minnesota Living with Heart Failure Questionnaire, an alternative measure of HF health status. These findings may have differed from our results because of differences in patient population as they enrolled participants with established HF, limited power due to fewer participants, and use of instruments with different test characteristics than the KCCQ.[41,42] Our results in this study, which found significant cross-sectional associations of GDF-15 and galectin-3 and health status consistent with early HF support the growing evidence of the association between newer cardiac biomarkers and patient-reported outcomes.

Contrary to our hypotheses, we did not find a significant association between hsTnT or NT-proBNP with cross-sectional KCCQ scores after adjustment for potential confounders. Similarly, studies in HF outpatients found bivariate correlations of NT-proBNP with health status scores, as measured by the Short Form 36 and KCCQ, but did not demonstrate an association after adjusting for covariates.[43,44] The authors concluded that "elevated BNP seems not to be sensed by the individual," suggesting differing roles of NT-proBNP over time in pathogenesis of HF versus the patient experience. Other studies in 342 and 163 HF outpatients, respectively, found that BNP levels were not correlated with baseline KCCQ scores, but they may have been underpowered.[45,46] In our study, it is possible that some of the variables in the models, such as cardiovascular medication use, may have been on the causal pathways of the associations.

In our study, we found significant associations of baseline GDF-15, hsTnT, and NT-proBNP levels with longitudinal decline in health status. The KCCQ measured longitudinally is an accepted clinical trial outcome and is informative of changes in clinical status.[23–25] Previous studies have not examined GDF-15 with KCCQ scores longitudinally. A secondary analysis of the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial found that NT-proBNP levels were associated with changes in KCCQ scores over 8 months.[47] The associations of GDF-15, hsTnT, and NT-proBNP with longitudinal KCCQ scores have several implications. Elevations in cardiac biomarkers may signal early pathophysiology and serve to identify patients at greatest risk for a decline in health status. Predicting health status as measured by KCCQ scores could be potentially useful because abnormal HF health status may be modifiable. Educational, exercise, and medical therapies have proven effective in improving KCCQ scores.[23,48,49] Interventions such as cardiac rehabilitation, which is known to improve health status in HF patients, have also been found to modify levels of galectin-3 and sST-2 over time, further underscoring

the relationships between cardiac biomarkers and health status.[50]

Our study has several strengths. We had a large sample size that was well powered to detect an association of cardiac biomarkers with KCCQ scores. We investigated longitudinal KCCQ scores over a 4-year time frame, evaluating the role of cardiac biomarkers in prognosticating the development of low KCCQ scores, as a marker of health status consistent with early HF. We also recognize limitations to our results. Our study is observational, so we are unable to determine causality and our analyses may be subject to residual confounding. Study participants were volunteers, which may limit generalizability to the broader CKD population. We were not able to study the effects of interventions in this study on improving HF health status or their effects on cardiac biomarkers. It is possible that the biomarkers may be associated with lower KCCQ scores via additional noncardiac mechanisms, such as inflammation, malignancy, and pulmonary disease.[51,52]

In summary, in a large, longitudinal cohort of CKD patients without HF, we found a significant association between GDF-15 and galectin-3 and health status consistent with early HF as measured by the KCCQ. We also found associations of GDF-15, hsTnT, and NT-proBNP with incident decline in KCCQ scores over time. Our findings provide further insights toward a better pathophysiologic understanding of the development of HF in CKD patients. Cardiac biomarkers, particularly GDF-15, could be useful for assessing and predicting health status consistent with early HF in patients with CKD.

APPENDIX

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Disclosures

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Supporting Information

Tables S1–S7

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SUPPLEMENTAL MATERIAL

Table S1. Demographic characteristics by quintile of galectin-3 (N = 2873).

	Quintile 1 ≤ 9.11 pg/mL (N = 576)	**Quintile 2 9.12 – 12.2 pg/mL (N = 573)**	**Quintile 3 12.3 – 15.4 pg/mL (N = 575)**	**Quintile 4 15.5 – 20.1 pg/mL (N = 574)**	**Quintile 5 > 20.1 pg/mL (N = 575)**
Demographics					
Age	57 (10.9)	59 (11.3)	59 (10.7)	60 (10.7)	61 (10.1)
Male	376 (65)	345 (60)	300 (52)	298 (52)	239 (42)
Race/ethnicity					
Non-Hispanic white	341 (59)	296 (52)	266 (46)	224 (39)	187 (33)
Non-Hispanic black	179 (31)	197 (34)	232 (40)	236 (41)	267 (46)
Hispanic	32 (6)	51 (9)	55 (10)	86 (15)	100 (17)
Other	24 (4)	29 (5)	22 (4)	28 (5)	21 (4)
Comorbidities					
Cardiovascular disease	125 (22)	140 (24)	157 (27)	171 (30)	213 (37)
MI/prior revascularization	83 (14)	100 (17)	106 (18)	110 (19)	131 (23)
COPD	21 (4)	28 (5)	22 (4)	22 (4)	28 (5)
Atrial fibrillation	72 (12)	89 (16)	75 (13)	87 (15)	96 (17)
Stroke	42 (7)	37 (6)	57 (10)	59 (10)	74 (13)
Diabetes	206 (36)	211 (37)	263 (46)	296 (52)	365 (63)
Clinical variables					
Systolic blood pressure (mmHg)	120.2 (19.7)	124.1 (19.4)	126.0 (21.0)	129.7 (22.2)	132.2 (22.2)
BMI (kg/m^2)	31 (6.4)	31 (7.6)	32 (7.2)	33 (8.1)	34 (8.3)
Current smoking	41 (7)	59 (10)	88 (15)	67 (12)	85 (15)
Laboratory and imaging variables					
eGFR (CKD-EPI) ($mL/min/1.73m^2$)	51.8 (15.2)	45.8 (15.0)	43.8 (15.1)	39.4 (13.8)	35.0 (14.0)
Urinary protein to creatinine ratio from 24hr urine test	74 (41-259)	93 (46-513)	113 (53-577)	144 (58-622)	339 (83-1330)
Ejection fraction (%)	54.9 (7.4)	55.5 (7.1)	55.5 (7.3)	55.2 (7.5)	55.2 (7.0)
Left ventricular mass index (g)	57.5 (20.3)	61.9 (21.5)	61.9 (21.8)	65.0 (23.1)	68.6 (23.4)
Medications					
ACEi/ARB	361 (63)	391 (68)	397 (69)	408 (71)	415 (72)
Diuretics	253 (44)	301 (53)	300 (52)	372 (65)	390 (68)
Beta blockers	221 (38)	258 (45)	264 (46)	301 (52)	305 (53)

Entries are mean (SD) for continuous covariates or N (%) for categorical covariates, except as noted.
MI – myocardial infarction; COPD – chronic obstructive pulmonary disease; BMI – body mass index; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

Table S2. Demographic characteristics by quintile of sST-2 (N = 2873).

	Quintile 1 ≤ 10.4 pg/mL (N = 577)	**Quintile 2 10.5 – 13.4 pg/mL (N = 573)**	**Quintile 3 13.5 – 16.8 pg/mL (N = 574)**	**Quintile 4 16.9 – 22 pg/mL (N = 574)**	**Quintile 5 > 22 pg/mL (N = 575)**
Demographics					
Age	57 (11.6)	59 (10.1)	60 (10.6)	60 (10.6)	60 (10.9)
Male	227 (39)	264 (46)	299 (52)	369 (64)	399 (69)
Race/ethnicity					
Non-Hispanic white	237 (41)	270 (47)	262 (46)	265 (46)	280 (49)
Non-Hispanic black	254 (44)	238 (42)	227 (40)	203 (35)	189 (33)
Hispanic	53 (9)	46 (8)	63 (11)	79 (14)	83 (14)
Other	33 (6)	19 (3)	22 (4)	27 (5)	23 (4)
Comorbidities					
Cardiovascular disease	108 (19)	161 (28)	152 (26)	188 (33)	197 (34)
MI/prior revascularization	65 (11)	104 (18)	96 (17)	129 (22)	136 (24)
COPD	25 (4)	27 (5)	23 (4)	19 (3)	27 (5)
Atrial fibrillation	64 (11)	93 (16)	86 (15)	89 (16)	87 (15)
Stroke	39 (7)	55 (10)	57 (10)	57 (10)	61 (11)
Diabetes	193 (33)	242 (42)	250 (44)	321 (56)	335 (58)
Clinical variables					
Systolic blood pressure (mmHg)	123.1 (19.9)	124.2 (20.1)	126.1 (20.9)	130.4 (22.9)	128.4 (21.9)
BMI (kg/m^2)	32 (7.7)	32 (7.8)	32 (7.3)	32 (7.9)	31 (7.3)
Current smoking	80 (14)	67 (12)	69 (12)	61 (11)	63 (11)
Laboratory and imaging variables					
eGFR (CKD-EPI) ($mL/min/1.73m^2$)	46.4 (16.6)	44.2 (15.3)	44.1 (15.2)	41.4 (15.7)	39.6 (14.8)
Urinary protein to creatinine ratio from 24hr urine test	78 (44-295)	99 (47-380)	98 (48-484)	183 (60-885)	293 (78-1303)
Ejection fraction (%)	55.9 (7.3)	55.2 (7.2)	55.4 (7.3)	55.1 (7.4)	54.7 (7.1)
Left ventricular mass index (g)	59.6 (22.5)	62.0 (22.3)	62.5 (22.5)	65.5 (21.7)	64.7 (22.0)
Medications					
ACEi/ARB	352 (61)	401 (70)	393 (68)	421 (73)	405 (70)
Diuretics	274 (47)	319 (56)	306 (53)	351 (61)	366 (64)
Beta blockers	228 (40)	246 (43)	275 (48)	289 (50)	311 (54)

Entries are mean (SD) for continuous covariates or N (%) for categorical covariates, except as noted.
MI – myocardial infarction; COPD – chronic obstructive pulmonary disease; BMI – body mass index; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

Table S3. Demographic characteristics by category of hsTNT (N = 2873).

	<LLD ≤ 10 ng/L (N = 1023)	**Tertile 1 10.1 – 14.7 ng/L (N = 572)**	**Tertile 2 14.8 – 23.9 ng/L (N = 631)**	**Tertile 3 >23.9 ng/L (N = 647)**
Demographics				
Age	55 (11.4)	60 (10.1)	62 (9.8)	61 (9.6)
Male	357 (35)	309 (54)	407 (65)	485 (75)
Race/ethnicity				
Non-Hispanic white	526 (51)	296 (52)	280 (44)	212 (33)
Non-Hispanic black	349 (34)	198 (35)	257 (41)	307 (47)
Hispanic	89 (9)	58 (10)	69 (11)	108 (17)
Other	59 (6)	20 (3)	25 (4)	20 (3)
Comorbidities				
Cardiovascular disease	169 (17)	142 (25)	223 (35)	272 (42)
MI/prior revascularization	107 (10)	98 (17)	150 (24)	175 (27)
COPD	42 (4)	15 (3)	33 (5)	31 (5)
Atrial fibrillation	116 (11)	75 (13)	114 (18)	114 (18)
Stroke	63 (6)	46 (8)	76 (12)	84 (13)
Diabetes	267 (26)	240 (42)	344 (55)	490 (76)
Clinical variables				
Systolic blood pressure (mmHg)	120.1 (18.5)	124.9 (20.2)	130.5 (22.2)	133.9 (22.3)
BMI (kg/m^2)	31 (7.6)	32 (7.5)	33 (7.9)	33 (7.1)
Current smoking	119 (12)	73 (13)	70 (11)	78 (12)
Laboratory and imaging variables				
eGFR (CKD-EPI) ($mL/min/1.73m^2$)	50.2 (15.8)	43.6 (13.6)	40.0 (13.5)	34.6 (14.1)
Urinary protein to creatinine ratio from 24hr urine test	72 (42-218)	92 (49-350)	155 (63-745)	472 (128-1931)
Ejection fraction (%)	56.0 (6.3)	56.0 (7.2)	54.7 (7.7)	53.7 (8.1)
Left ventricular mass index (g)	53.6 (16.6)	61.4 (19.2)	67.5 (22.9)	75.9 (25.3)
Medications				
ACEi/ARB	616 (60)	408 (71)	475 (75)	473 (73)
Diuretics	419 (41)	314 (55)	405 (64)	478 (74)
Beta blockers	374 (37)	268 (47)	333 (53)	374 (58)

Entries are mean (SD) for continuous covariates or N (%) for categorical covariates, except as noted.
LLD - Lower Limit of Detection; MI – myocardial infarction; COPD – chronic obstructive pulmonary disease; BMI – body mass index; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

Table S4. Demographic characteristics by quintile of NT-proBNP (N = 2873).

	Quintile 1 ≤ 30.9 pg/mL (N = 575)	Quintile 2 31 – 76 pg/mL (N = 574)	Quintile 3 76.1 – 158 pg/mL (N = 575)	Quintile 4 158.1 – 370 pg/mL (N = 574)	Quintile 5 > 370 pg/mL (N = 575)
Demographics					
Age	54 (11.4)	58 (10.7)	60 (10.7)	61 (10.0)	62 (9.4)
Male	376 (65)	296 (52)	311 (54)	264 (46)	311 (54)
Race/ethnicity					
Non-Hispanic white	253 (44)	264 (46)	277 (48)	290 (51)	230 (40)
Non-Hispanic black	257 (45)	234 (41)	216 (38)	191 (33)	213 (37)
Hispanic	34 (6)	48 (8)	63 (11)	69 (12)	110 (19)
Other	31 (5)	28 (5)	19 (3)	24 (4)	22 (4)
Comorbidities					
Cardiovascular disease	76 (13)	112 (20)	156 (27)	182 (32)	280 (49)
MI/prior revascularization	46 (8)	65 (11)	96 (17)	129 (22)	194 (34)
COPD	15 (3)	25 (4)	19 (3)	34 (6)	28 (5)
Atrial fibrillation	52 (9)	62 (11)	74 (13)	90 (16)	141 (25)
Stroke	25 (4)	42 (7)	52 (9)	67 (12)	83 (14)
Diabetes	197 (34)	248 (43)	268 (47)	290 (51)	338 (59)
Clinical variables					
Systolic blood pressure (mmHg)	120.1 (17.7)	123.1 (19.2)	125.0 (20.4)	130.1 (22.1)	134.0 (23.8)
BMI (kg/m^2)	32 (7.0)	32 (7.1)	32 (7.7)	32 (8.4)	32 (7.7)
Current smoking	53 (9)	57 (10)	62 (11)	72 (13)	96 (17)
Laboratory and imaging variables					
eGFR (CKD-EPI) ($mL/min/1.73m^2$)	53.3 (14.6)	46.5 (14.5)	42.8 (15.1)	39.6 (13.7)	33.5 (13.2)
Urinary protein to creatinine ratio from 24hr urine test	69 (42-214)	96 (48-456)	128 (54-543)	140 (56-739)	329 (85-1390)
Ejection fraction (%)	55.6 (6.3)	56.2 (6.2)	55.6 (6.9)	55.4 (7.4)	53.2 (9.0)
Left ventricular mass index (g)	55.2 (17.6)	59.3 (20.1)	62.0 (21.4)	62.9 (20.9)	76.3 (25.8)
Medications					
ACEi/ARB	394 (69)	387 (67)	416 (72)	390 (68)	385 (67)
Diuretics	246 (43)	294 (51)	330 (57)	343 (60)	403 (70)
Beta blockers	150 (26)	215 (37)	258 (45)	336 (59)	390 (68)

Entries are mean (SD) for continuous covariates or N (%) for categorical covariates, except as noted.
MI – myocardial infarction; COPD – chronic obstructive pulmonary disease; BMI – body mass index; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; ACEi – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

Table S5. Correlations of log-transformed biomarkers adjusted for age and sex.

	GDF-15	Galectin-3	sST-2	hsTnT	NT-proBNP
GDF-15	1.00	0.35	0.28	0.32	0.31
Galectin-3		1.00	0.12	0.17	0.15
sST-2			1.00	0.13	0.11
hsTnT				1.00	0.24
NT-proBNP					1.00

Entries are the partial correlation between the log-transformed biomarkers adjusting for age and sex.

Table S6. Effect of adjustment for LV mass index, ejection fraction, and baseline KCCQ scores on the associations of biomarkers with year 1 KCCQ <75 and incident decline in KCCQ scores.

		Model 2	Model 3	Model 4	Model 5
GDF-15 Continuous Model	KCCQ <75 OR (99% CI)	1.42 (1.19, 1.68)*	1.33 (1.12, 1.59)*	1.41 (1.19, 1.68)*	--
Log(GDF-15) per 1 SD (0.58 pg/mL) increase	Incident Decline in KCCQ HR (99% CI)	1.36 (1.12, 1.65)*	1.32 (1.07, 1.61)*	1.34 (1.11, 1.63)*	1.24 (1.01, 1.52)*
Galectin-3 Continuous Model	KCCQ <75 OR (99% CI)	1.28 (1.12, 1.48)*	1.23 (1.07, 1.41)*	1.29 (1.12, 1.48)*	--
Log(Galectin-3) per 1 SD (0.50 pg/mL) increase	Incident Decline in KCCQ^ HR (99% CI)	1.08 (0.92, 1.26)	1.05 (0.90, 1.23)	1.08 (0.92, 1.26)	1.06 (0.91, 1.23)
sST-2 Continuous Model	KCCQ <75 OR (99% CI)	1.12 (0.98, 1.28)	1.07 (0.94, 1.21)	1.12 (0.98, 1.28)	--
Log(sST-2) per 1 SD (0.55 pg/mL) increase	Incident Decline in KCCQ HR (99% CI)	1.08 (0.92, 1.26)	1.04 (0.90, 1.22)	1.08 (0.93, 1.27)	1.04 (0.89, 1.22)
hsTnT Continuous Model	KCCQ <75 OR (99% CI)	1.10 (0.93, 1.31)	1.01 (0.85, 1.20)	1.10 (0.92, 1.30)	--
Log(hsTnT) per 1 SD (0.78 ng/L) increase	Incident Decline in KCCQ HR (99% CI)	1.20 (1.01, 1.44)*	1.15 (0.95, 1.39)	1.17 (0.97, 1.40)	1.17 (0.98, 1.40)
NT-proBNP Continuous Model	KCCQ <75 OR (99% CI)	1.03 (0.88, 1.21)	0.97 (0.83, 1.14)	1.02 (0.87, 1.20)	--
Log(NT-proBNP) per 1 SD (1.60pg/mL) increase	Incident Decline in KCCQ HR (99% CI)	1.30 (1.08, 1.56)*	1.26 (1.04, 1.51)*	1.25 (1.04, 1.51)*	1.23 (1.02, 1.47)*

*P< 0.01

Model 2: Age, sex, race/ethnicity (M1) + myocardial infarction, chronic obstructive pulmonary disease, atrial fibrillation, stroke, baseline diabetes, systolic blood pressure, body mass index, current smoking, eGFR, 24 hour urinary protein, ACEi/ARBs, diuretics, and beta blocker use.

Model 3: M2 + other cardiac biomarkers.

Model 4: M2 + LV Mass Index and Ejection Fraction.

Model 5: M2 + Year 1 KCCQ score.

^Incident Decline in KCCQ defined as participants with KCCQ≥75 developing a KCCQ < 75 and having an average decline in KCCQ score of >3 points/year.

N = 2873 for year 1 KCCQ analysis.

N = 2132 for analysis of incident decline in KCCQ scores at year 5.

LV – left ventricular; KCCQ – Kansas City Cardiomyopathy Questionnaire; HF – heart failure; OR – odds ratio; CI – confidence interval; LLD - Lower Limit of Detection

Table S7. Association of cardiac biomarkers with incident decline in KCCQ scores†, among participants with year 1 KCCQ ≥ 60 (N = 2461).

	Incident Decline in KCCQ† Model 0 HR (99% CI)	Incident Decline in KCCQ Model 1 aHR (99% CI)	Incident Decline in KCCQ Model 2 aHR (99% CI)
GDF-15 Continuous Model Log(GDF-15) per 1 SD (0.58 pg/mL) increase	1.65 (1.39, 1.95)*	1.58 (1.31, 1.89)*	1.41 (1.13, 1.76)*
GDF-15 Categorical Model			
Quintile 1 (≤ 856 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (857 – 1200 pg/mL)	2.01 (1.05, 3.85)*	1.88 (0.97, 3.65)	1.69 (0.84, 3.37)
Quintile 3 (1201 – 1570 pg/mL)	2.79 (1.49, 5.23)*	2.65 (1.39, 5.05)*	2.11 (1.05, 4.24)*
Quintile 4 (1571 – 2220 pg/mL)	3.70 (1.99, 6.86)*	3.39 (1.77, 6.50)*	2.32 (1.10, 4.89)*
Quintile 5 (> 2220 pg/mL)	5.04 (2.72, 9.35)*	4.59 (2.39, 8.81)*	3.37 (1.57, 7.23)*
Galectin-3 Continuous Model Log(Galectin-3) per 1 SD (0.50 pg/mL) increase	1.33 (1.11, 1.58)*	1.17 (0.98, 1.40)	1.03 (0.86, 1.23)
Galectin-3 Categorical Model			
Quintile 1 (≤ 9.11 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (9.12 – 12.2 pg/mL)	1.58 (0.89, 2.78)	1.42 (0.80, 2.51)	1.31 (0.74, 2.34)
Quintile 3 (12.3 – 15.4 pg/mL)	1.80 (1.03, 3.16)*	1.53 (0.87, 2.69)	1.32 (0.75, 2.32)
Quintile 4 (15.5 – 20.1 pg/mL)	2.08 (1.20, 3.62)*	1.61 (0.92, 2.82)	1.22 (0.69, 2.16)
Quintile 5 (> 20.1 pg/mL)	2.57 (1.47, 4.49)*	1.83 (1.03, 3.24)*	1.28 (0.71, 2.30)
sST-2 Continuous Model Log(sST-2) per 1 SD (0.55 pg/mL) increase	1.16 (0.97, 1.38)	1.24 (1.02, 1.49)*	1.14 (0.93, 1.38)
sST-2 Categorical Model			
Quintile 1 (≤ 10.4 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (10.5 – 13.4 pg/mL)	1.42 (0.84, 2.41)	1.50 (0.88, 2.56)	1.25 (0.73, 2.14)
Quintile 3 (13.5 – 16.8 pg/mL)	1.41 (0.83, 2.42)	1.53 (0.89, 2.63)	1.24 (0.72, 2.14)
Quintile 4 (16.9 – 22 pg/mL)	1.39 (0.80, 2.40)	1.58 (0.91, 2.77)	1.13 (0.64, 2.00)
Quintile 5 (> 22 pg/mL)	1.59 (0.93, 2.72)	2.01 (1.15, 3.50)*	1.58 (0.90, 2.79)
hsTnT Continuous Model Log(hsTnT) per 1 SD (0.78 ng/L) increase	1.41 (1.19, 1.66)*	1.48 (1.24, 1.77)*	1.25 (1.01, 1.56)*
hsTnT Categorical Model			
< LLD (< 10 ng/ L)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Tertile 1 (10.1 – 14.7 ng/L)	1.38 (0.87, 2.20)	1.51 (0.93, 2.43)	1.25 (0.76, 2.04)
Tertile 2 (14.8 – 23.9 ng/L)	1.47 (0.93, 2.33)	1.66 (1.02, 2.71)*	1.17 (0.70, 1.97)
Tertile 3 (> 23.9 ng/L)	2.50 (1.62, 3.84)*	2.90 (1.79, 4.69)*	1.90 (1.10, 3.26)*
NT-proBNP Continuous Model Log(NT-proBNP) per 1 SD (1.60 pg/mL) increase	1.46 (1.22, 1.75)*	1.40 (1.16, 1.69)*	1.14 (0.91, 1.41)
NT-proBNP Categorical Model			
Quintile 1 (≤ 31.9 pg/mL)	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)
Quintile 2 (31 – 76 pg/mL)	1.19 (0.67, 2.10)	1.12 (0.63, 1.99)	0.99 (0.55, 1.79)
Quintile 3 (76.1 – 158 pg/mL)	1.39 (0.79, 2.44)	1.32 (0.74, 2.33)	0.98 (0.54, 1.77)
Quintile 4 (158.1 – 370 pg/mL)	1.92 (1.12, 3.29)*	1.84 (1.05, 3.20)*	1.27 (0.71, 2.30)
Quintile 5 (> 370 pg/mL)	2.78 (1.64, 4.69)*	2.41 (1.39, 4.16)*	1.43 (0.77, 2.66)

*$P < 0.01$

†Incident Decline in KCCQ defined as participants with KCCQ≥60 developing a KCCQ <60 and having an average decline in KCCQ score of >5 points/year.

Model 0: Unadjusted.
Model 1: Age, sex, race/ethnicity.
Model 2: M1 + myocardial infarction, chronic obstructive pulmonary disease, atrial fibrillation, stroke, baseline diabetes, systolic blood pressure, body mass index, current smoking, eGFR, 24h urinary protein, ACEi/ARBs, diuretics, and beta blocker use.
HF – heart failure; KCCQ – Kansas City Cardiomyopathy Questionnaire; HR – hazard ratio; CI – confidence interval; aHR – adjusted hazard ratio;LLD - Lower Limit of Detection