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Circulating Procollagen type III N-terminal Peptide and Mortality Risk in African Americans with Heart Failure

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Abstract

Background—Procollagen type III N-terminal peptide (PIIINP) is a biomarker of cardiac fibrosis that is associated with heart failure prognosis in Caucasians. Its prognostic significance in African Americans is unknown. We sought to determine whether PIIINP is associated with outcomes in African Americans with heart failure.

Methods and Results—Blood was collected from 138 African Americans with heart failure for determining PIIINP and genetic ancestry, and patients were followed prospectively for death or hospitalization for heart failure. PIIINP was inversely correlated with West African ancestry (R^2=0.061, p=0.010). PIIINP >4.88 ng/ml was associated with all-cause mortality on univariate (hazard ratio: 4.9, 95% confidence interval: 2.2–11.0; p<0.001) and multivariate (HR: 5.8; 1.9–17.3; p=0.002) analyses over a median follow-up period of 3 years. We also observed an increased risk for the combined outcome of all-cause mortality or hospitalization for heart failure with PIIINP >4.88 ng/ml on univariate (HR: 2.6; 95% CI 1.6–5.0; p<0.001) and multivariate (HR 2.4; 95% CI: 1.2–4.7; p-0.016) analyses.

Conclusion—High circulating PIIINP is associated with poor outcomes in African Americans with chronic heart failure, suggesting that PIIINP may be useful in identifying African Americans who may benefit from additional therapy to combat fibrosis as a means of improving prognosis.

Keywords

heart failure; African American; fibrosis

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Introduction

There are significant ethnic differences in heart failure susceptibility, etiology, and prognosis. For example, African Americans have a higher incidence of heart failure, are less likely to have obstructive coronary disease as a cause for heart failure, and have higher mortality rates from the disease compared to Caucasians.[1–8] There is additional evidence suggesting ethnic variability in response to heart failure medications, which could potentially be secondary to differences in heart failure pathophysiology by ethnicity.[9–11]

Cardiac fibrosis is an important component of cardiac remodeling and contributes to the progression of heart failure regardless of etiology.[12] Cardiac fibrosis is a major determinant of myocardial stiffness, left ventricular contractility, and risk for cardiac arrhythmias.[13–15] Medications that attenuate cardiac fibrosis, including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs), reduce cardiac fibrosis and significantly reduce morbidity and mortality in patients with heart failure and reduced ejection fraction (EF).[16–23]

Type III collagen is one of the primary collagen types that contribute to cardiac fibrosis.[24] Procollagen type III N-terminal peptide (PIIINP) is released into the bloodstream when type III collagen is incorporated into the myocardium and has been correlated with the degree of type III collagen deposition.[25, 26] While a number of circulating biomarkers have been proposed for noninvasive assessment of cardiac fibrosis, PIIINP is one of the few biomarkers correlated with myocardial collagen volume fraction. [26, 27] Circulating PIIINP is also correlated with risks for hospitalization and death in largely Caucasian cohorts with heart failure. Additional evidence shows that PIIINP is predictive of response to therapies that attenuate fibrosis, such as ACE inhibitors and MRAs.[16, 28] For example, the greatest survival benefits with MRA therapy in heart failure have been observed in patients with the highest PIIINP levels at baseline.[16]

There is a paucity of data on the prognostic significance of PIIINP in African Americans. Because of significant differences in heart failure susceptibility, etiology, and prognosis by ethnicity, it is important to confirm that prognostic indicators in Caucasians extend to African Americans. Insight into factors associated with death or hospitalization in African Americans with heart failure could lead to better treatment strategies to improve outcomes in this population. In particular, an enhanced understanding of collagen turnover and its relevance to heart failure outcomes in African Americans may better define the role of therapies to combat cardiac fibrosis in this population, who has been significantly underrepresented in most heart failure studies to date. Therefore, we sought to determine whether PIIINP is associated with risk for death or the combined outcome of death or hospitalization for heart failure among African Americans with heart failure.

Materials and methods

Patient population and procedures

A total of 138 African Americans, age ≥18 years, with a history of Stage C heart failure were enrolled from the heart failure clinic at the University of Illinois Hospital & Health Sciences System (UI-Health) between November 2001 and February 2014. These patients were part of a larger cohort of patients enrolled in a heart failure research database. Additional inclusion criteria for the current study included class I through III New York Heart Association (NYHA) functional status, treatment with guideline-driven medical therapy with an ACE inhibitor (or ARB) and β-blocker, in the absence of a history of medication intolerance,[29] and absence of heart failure-related hospitalization for at least 3 months prior to enrollment. Patients unable to tolerate an ACE inhibitor or ARB were included if they were taking hydralazine plus nitrates. Patients taking an MRA were excluded to avoid confounding effects of an MRA on circulating PIIINP. Patients with a history of rheumatoid arthritis, pulmonary fibrosis, metabolic bone disease, active malignancy, or acute coronary syndrome within 3 months were also excluded to minimize the likelihood of diseases of than heart failure contributing to circulating PIIINP. The study protocol was approved by the University of Illinois at Chicago Institutional Review Board, and all patients provided written, informed consent for study participation.

On the day of enrollment, a cardiologist performed a medical history and physical examination, and a clinical pharmacist obtained a medication history. Blood samples were obtained for determination of serum PIIINP and individual genetic ancestry. All samples were obtained between 8 am and 1 pm. Demographic and clinical data were recorded from the electronic medical record and through patient interview. Hospital admissions for heart failure were tracked prospectively through patient interview and review of the electronic health record at each heart failure clinic visit. Admission, consult, and discharge summary notes were used to determine if the hospitalization occurring at UI Health was heart failure related. Hospitalizations at outside institutions were assessed through patient interview at each clinic visit. Deaths were assessed through medical record review and the Social Security Death Index.

Serum PIIINP measurement

Serum PIIINP was determined by radioimmunoassay using a commercially available kit containing I-125-labeled procollagen (Orion Diagnostica, Finland; distributed by Immunodiagnostic Systems Inc., Scottsdale, AZ). Assay sensitivity was 0.3 μg/L for PIIINP. Intra- and interassay coefficients of variation were 2.8% and 2.5%, respectively.

Genetic ancestry

Individual genetic ancestry was determined for each person using 105 autosomal DNA ancestry informative markers for West African, Native American, and European genetic ancestry using published methods, to confirm African descent.[30, 31] Our group [32] and others [33] have demonstrated that approximately 100 ancestry informative markers are required to obtain estimates of ancestry that correlate with the true individual ancestral proportions with correlation coefficients more than 0.9. Individual ancestry was estimated

from the genotype data using the Bayesian Markov Chain-Monte Carlo (MCMC) method implemented in the program STRUCTURE version 2.1.[34, 35] STRUCTURE as run under the admixture model using prior population information and independent allele frequencies. Each participant was scored from 0% to 100% for individual estimates of West African, Native American and European ancestry.

Statistical analysis

The association between serum PIIINP and West African ancestry was determined via Pearson correlational analysis. Baseline PIIINP levels were compared between patients who died and those who survived as well as between those who died or were hospitalized for heart failure versus those with hospitalization-free survival over the course of follow-up using the Student's unpaired *t*-test. Receiver operating characteristic (ROC) curves were used to determine the optimal dichotomization point of PIIINP to predict all-cause mortality and the composite of death or hospitalization for heart failure. The area under the ROC curve is a measure of PIIINP accuracy or ability to discriminate risk. The cut point was selected as the point that yielded the best sensitivity and specificity combination. Clinical characteristics were compared between patients with a PIIINP level above and below the cut point value of 4.88 ng/ml as determined by the ROC curve, by the Chi-square test for categorical variables and Student's unpaired *t*-test for continuous variables. Univariate and multivariate Cox proportional hazards regression was used to calculate the hazard ratios for each outcomes associated with PIIINP, modeled as a continuous or dichotomous variable. Variables significantly correlated with outcomes on univariate analysis ($p<0.05$) or known to influence outcomes were incorporated into the multivariate analyses. The proportional hazard assumption of the Cox regression was tested by the interaction between time to event and PIIINP. The contribution of PIIINP to outcomes was assessed by the Likelihood Ratio Test of the goodness-of-fit between models with and without PIIINP. Net reclassification improvement and integrated discriminatory improvement were also calculated using STATA IC13 (College Station, Texas) to quantify the improvement in the prediction model for outcomes when PIIINP was added as a dichotomous (net reclassification improvement) or continuous (integrated discriminatory improvement) variable.[36] Kaplan-Meier and log-rank tests were used to construct unadjusted survival curves for time to death from any cause and time to death or first hospitalization for heart failure between patients with a PIIINP level above and below the threshold value. Patients were censored from the analysis if an endpoint (death or hospitalization for heart failure) was reached or the patient was lost to follow-up. Secondary analyses were done for patients with a left ventricular EF <40%. Statistical analyses were conducted using IBM SPSS 21(Armonk, NY).

Results

Study population

The mean age of the study population was 57 ± 15 years, and the median West African ancestry was 79% (range 41% to 95%). The majority (78%) had a non-ischemic etiology for heart failure (33% with a hypertensive etiology), and the mean left ventricular EF of the study population was 36 ± 13%. Seventy-four (54%) patients had an EF <40% at baseline. Most patients (76%) had NYHA functional class II or III symptoms at the time of

enrollment, and none had class IV symptoms. Patients were well treated at enrollment; 92% were taking an ACE inhibitor or angiotensin receptor blocker, and 96% were taking a β-blocker. Sixty-one percent of β-blocker–treated patients were on guideline-directed target doses (i.e. metoprolol CR/XL 200 mg/day or carvedilol 50–100 mg/day).

The mean PIIINP level was 5.49 ± 3.09 ng/ml. The area under the ROC curve was 0.718 (p<0.001, Figure 1) for the prediction of mortality based on PIIINP concentration and 0.634 for prediction of all-cause mortality or first hospitalization for heart failure (p <0.001, Figure 2). The optimal PIIINP threshold value was 4.88 ng/ml, corresponding to a sensitivity of 0.75 and specificity of 0.63 for prediction of all-cause mortality, and 0.64 and 0.66, respectively for prediction of mortality or heart failure hospitalization. Serum PIIINP was above the threshold value of 4.88 ng/ml in 63 (46%) patients. Baseline characteristics of patients with a PIIINP level >4.88 ng/ml (high PIIINP group) or 4.88 ng/ml or below (low PIIINP group) are summarized in Table 1. Patients with higher PIIINP had a higher prevalence of ischemic heart disease, lower left ventricular EF, lower glomerular filtration rate (GFR), were less likely to be on a β-blocker, and tended to have a higher prevalence of atrial fibrillation.

Serum PIIINP and ancestry

For each 1% increase in West African ancestry, there was an associated 0.010 ng/ml lower PIIINP level (R^2=0.061, β coefficient −0.01; 95% CI −0.017 to −0.002; p=0.010). There was no significant association between West African ancestry and all-cause mortality (p=0.142) or the combined outcome of all-cause mortality or heart failure hospitalization (p=0.123).

Serum PIIINP and all-cause mortality

Median time to death or censoring was 3.14 years, with a median of 2.41 years for the higher PIIINP group and 3.62 years for the lower PIIINP group. Thirty-two (23%) patients died over the course of follow-up, consisting of 24 (38%) patients from the high PIIINP group and 8 (11%) from the low PIIINP group (p<0.001). The mean PIIINP level (measured at the time of enrollment) was 6.92 ± 2.92 ng/mL among patients who died and 5.06 ± 3.02 ng/mL among survivors (p=0.003).

In the unadjusted analysis, Kaplan-Meier survival curves (Figure 3) demonstrated significantly higher all-cause mortality in the higher serum PIIINP group (log-rank p<0.001). On univariate analysis, PIIINP concentration was associated with all-cause mortality when consider as either a continuous variable or a dichotomous variable using the cut-off point of 4.88 ng/mL (p <0.001 for both), as shown in Table 2. Additional variables associated with all-cause mortality on univariate analyses were older age, ischemic heart disease, history of atrial fibrillation or flutter, renal function, absence of β-blocker therapy, and reduced EF. Male sex also tended to be associated with increased mortality. After controlling for these factors and additional factors known to impact mortality (i.e. NYHA functional class),[37–41] PIIINP >4.88 ng/ml (p=0.002, Table 3) and as a continuous variable (p=0.010) was an independent predictor of all-cause mortality. PIIINP >4.88ng/ml was found to provide incremental prognostic value in predicting all-cause mortality by the Likelihood Ratio Test for goodness-of-fit (p<0.001). The net reclassification improvement

after adding PIIINP as a dichotomous variable to the adjusted prediction model for prediction of all-cause mortality was 71% (p=0.001), and the integrated discriminatory improvement was 4% (p=0.012). Among patients with an EF <40%, PIIINP >4.88 ng/ml remained associated with all-cause mortality on both univariate (p<0.001) and multivariate (p<0.001) analysis.

Serum PIIINP and all-cause mortality or heart failure hospitalizations

Median time to death or first heart failure hospitalization or censoring was 3.13 years with a median of 2.22 years for the higher PIIINP group and 3.52 years for the lower PIIINP group. Fifty-three (38%) patients died or were hospitalized for heart failure over the course of follow-up; 34 (54%) were in the higher PIIINP group and 19 (25%) were in the lower PIIINP group (p=0.001). The mean baseline PIIINP level among patients who died or were hospitalized for heart failure versus those with hospital-free survival was 6.77 ± 3.31 ng/mL and 4.70 ± 2.66 ng/mL, respectively (p<0.001).

Kaplan-Meier survival curves (Figure 4) demonstrated a significantly higher death or heart failure hospitalization rate among patients in the higher PIIINP group (log-rank p<0.001). Higher PIIINP serum levels were significantly associated with all-cause mortality or heart failure hospitalization when considered as a continuous or dichotomous variable using the cut-off point of 4.88 ng/mL (p<0.001 for both) on univariate analyses (Table 2). Additional variables associated with heart failure hospitalization were older age, history of atrial fibrillation or flutter, lower GFR, and absence of a βlocker use. Though not statistically significant, male sex and NYHA functional class tended to be associated with the combined outcome. After controlling for these factors and factors shown to impact risk for heart failure hospitalization (i.e. ischemic heart disease, EF),[37–39, 41] PIIINP remained a significant predictor of death or heart failure hospitalization when evaluated as a dichotomous (p=0.016) or continuous (p=0.024) variable (Table 3). PIIINP > 4.88ng/ml provided incremental prognostic value in predicting the combined outcome by the Likelihood Ratio Test for goodness-of-fit (p=0.018). The Net reclassification improvement and integrated discriminatory improvement after adding PIIINP as a dichotomous variable to the adjusted prediction model were 55% (p=0.004) and 2% (p=0.057), respectively. Similarly, among patients with an EF <40%, PIIINP >4.88 ng/ml was associated with death or heart failure hospitalization on univariate (p=<0.001) and multivariate (p<0.001) analysis.

Discussion

Our primary finding was that higher circulating PIIINP was associated with all-cause mortality and the combined outcome of all-cause mortality or hospitalization for heart failure in African Americans with chronic heart failure receiving standard vasodilator and β-blocker therapy. The higher risk for poor outcomes was evident whether PIIINP was assessed as a continuous or dichotomous variable, and PIIINP remained associated with risk for death and death or heart failure hospitalization after adjusting for clinical variables well known to influence heart failure prognosis.

To our knowledge, this is the first study to demonstrate an association between PIIINP and outcomes in African Americans with heart failure. Our findings are in agreement with

previous reports in predominately Caucasian populations.[16, 42] Specifically, post-hoc analysis of the Randomized Aldactone Evaluation Study (RALES), in which 98% of participants were Caucasian, showed that higher PIIINP levels (PIIINP >3.85 μg/L)were associated with increased risk for death (relative risk 2.3, 95% CI 1.34 to 4.18) and death or hospitalization (relative risk 1.83, 95% CI 1.18–2.83), and this risk was attenuated with the addition of spironolactone therapy.[16] The survival benefits of spironolactone were limited to patients with elevated PIIINP. Participants in RALES had NYHA class III or IV heart failure, whereas the majority of the patients in our study had class I or II symptoms, and none had class IV heart failure. Thus, in addition to showing a novel association between PIIINP and outcomes in African Americans, our findings extend the association between PIIINP and outcomes to patients with less severe heart failure.

Another notable difference between our cohort and the one in RALES is that only 11% of RALES participants were taking a β-blocker. In contrast nearly all patients in our study were on a β-blocker, in addition to an ACE inhibitor or ARB, as directed by heart failure guidelines.[29] β-blockers inhibit plasma renin release, and thus, like ACE inhibitors and ARBs, have been shown to reduce cardiac fibrosis in heart disease.[13, 17, 43–48] Yet, we found that PIIINP was elevated and associated with poor prognosis in a significant portion of African American patients.

By design, none of the patients in our study were taking a MRA, which when added to standard therapy has been shown to reduce morbidity and mortality in heart failure. [21, 49] However, data show that MRAs are significantly under prescribed, which may be due to uncertainty about whether their potential benefit outweighs risk for hyperkalemia and other adverse drug effects.[50–52] A recent analysis of RALES data showed that spironolactone reduced the combined end point of death or hospitalization for heart failure in Caucasians, but not in African Americans, which could lead to further uncertainty about MRA use in the latter group.[11] Interestingly, patients in our study with a higher degree of West African ancestry had lower serum PIIINP levels. This may provide insight into potential ethnic differences in drug response. Specifically, when taken into consideration with data that MRAs provide the greatest mortality benefit in patients with high PIIINP,[16] the negative correlation between PIIINP and West African ancestry provides a potential explanation for the lower MRA efficacy observed in African Americans compared to non-African Americans. Given evidence that higher PIIINP levels portend greater benefit from an MRA, the negative correlation between PIIINP and West African ancestry could potentially contribute to reduced MRA effectiveness in African Americans compared to other ethnic groups. Nonetheless, a significant portion of African Americans with heart failure had elevated PIIINP, which places them at an increased risk for mortality and thus, they would be expected to benefit from MRA therapy to combat fibrosis and potentially improve outcomes.

We excluded patients with many non-cardiac disorders known to influence procollagen levels to improve the likelihood that circulating PIIINP was reflective of myocardial collagen content. However, in the absence of cardiac biopsy, the gold standard for assessing fibrosis, we cannot confirm that PIIINP were truly reflective of cardiac collagen. Our population consisted of patients with stable heart failure on guideline-driven medical therapy

and free of recent hospitalization for heart failure, which likely explains the low event rate. Outcome data, particularly related to heart failure hospitalization, were collected from the medical record and through interview of patients during heart failure clinic visits. The latter was done to help identify heart failure admissions at outside institutions to better characterize out-of-system utilization which would not be captured through the medical chart review. However, outside admissions may have been missed because of poor patient recall or patient drop-out, which limits our findings regarding this endpoint. We did not measure other biomarkers, such as brain natriuretic peptide. However, PIIINP is a more specific marker for cardiac fibrosis, and elevated PIIINP suggests that additional therapy to attenuate cardiac fibrosis may be warranted. Finally, our findings are limited by the relatively small sample size and retrospective nature of the analysis and may not be representative of the broader African American population with heart failure. As such, additional data from larger and more diverse populations are necessary to validate the study findings.

Conclusion

In conclusion, we found that elevated PIIINP was associated with increased all-cause mortality in African Americans receiving standard vasodilator and β-blocker therapy for heart failure. Whether additional therapy that attenuates cardiac fibrosis will improve survival in African American patients with elevated PIIINP remains to be determined.

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Highlights

- Serum procollagen type III N-terminal peptide (PIIINP) is a biomarker of cardiac fibrosis.
- We evaluated the association between serum PIIINP and outcomes in African Americans with New York Heart Association Class I through Class III heart failure.
- On multi-variate analysis, PIIINP >4.88 ng/ml was a significant predictor of all-cause mortality (hazard ratio: 5.8, 95% confidence interval: 1.9–17.3; p=0.002) and the combined outcome of all-cause mortality or hospitalization for heart failure (HR: 2.4, 95% CI 1.2–4.7; p=0.016).
- PIIINP may be a useful biomarker for identifying African Americans who may benefit from additional therapy to attenuate cardiac fibrosis and potentially improve outcomes.

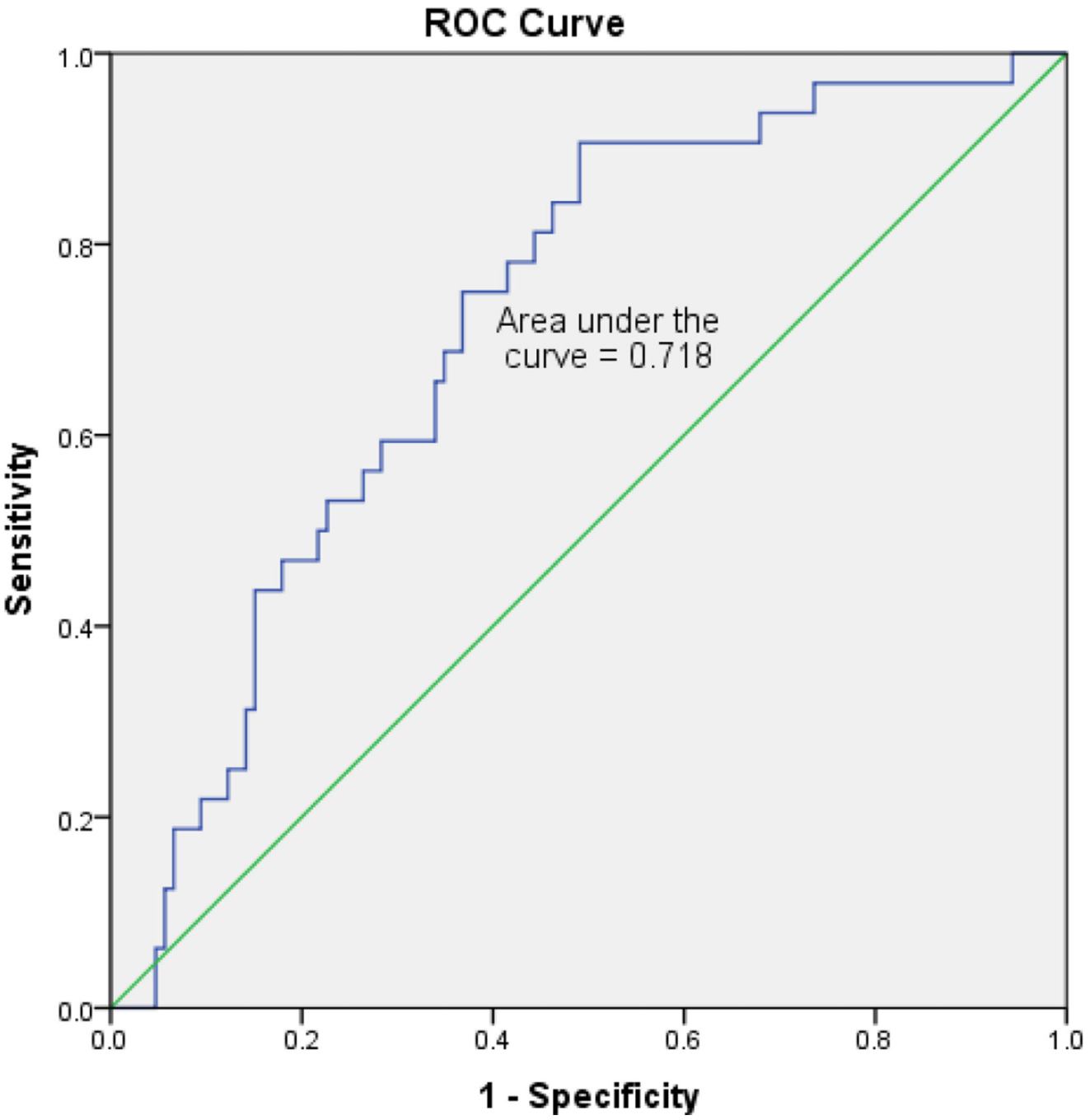

Figure 1.
Receiver operation characteristic curves for the prediction of mortality based on procollagen type III N-terminal peptide levels. ($p<0.001$ for the area under the curve versus a non-discriminatory area under the curve of 0.50)

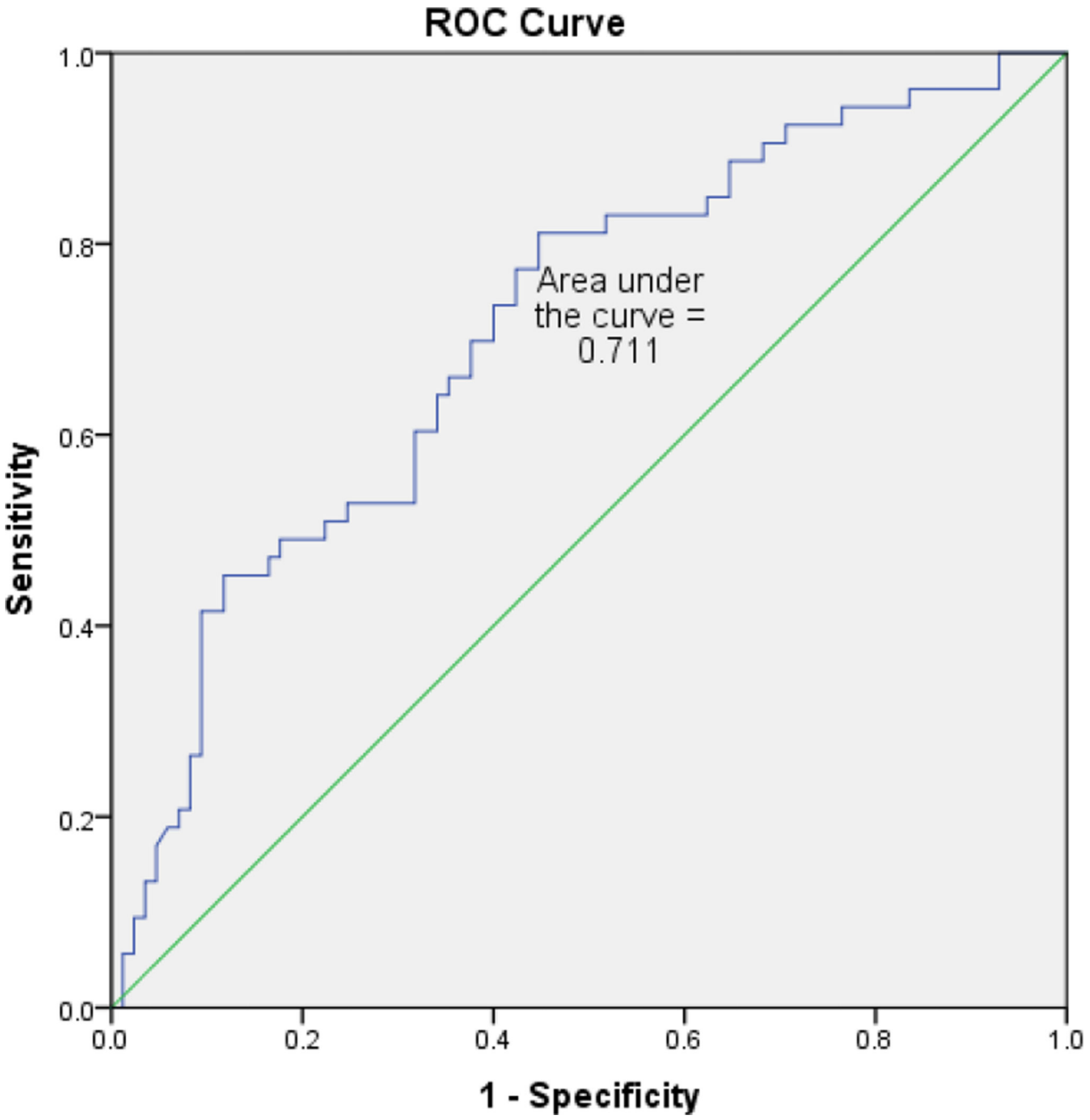

Figure 2.
Receiver operation characteristic curves for the prediction of all-cause mortality or heart failure hospitalization based on PIIINP levels ($p<0.001$ for the area under the curve versus a non-discriminatory area under the curve of 0.50)

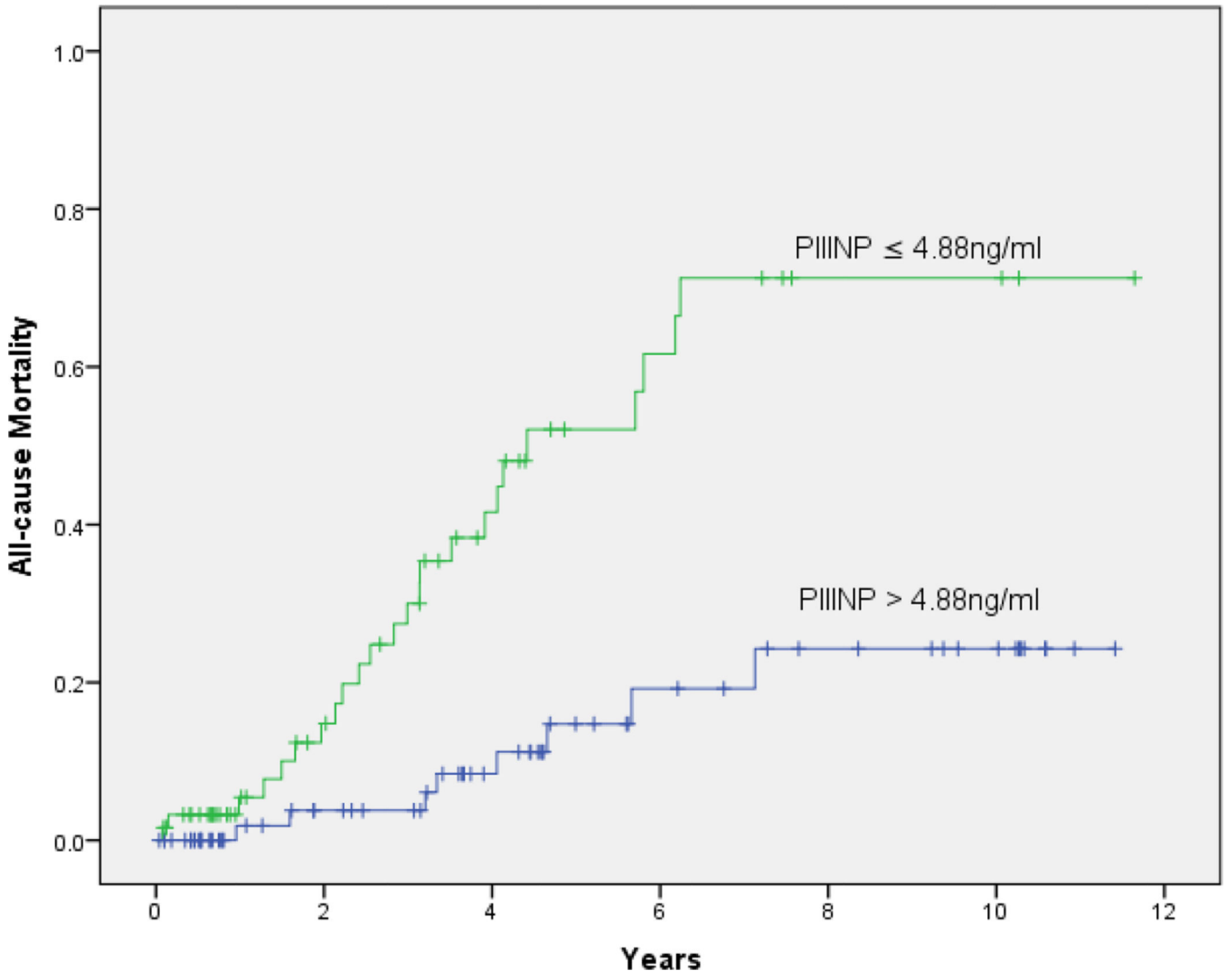

Figure 3.

Kaplan-Meier curves of all-cause mortality for patients stratified by procollagen type III N-terminal peptide (PIIINP) > 4.88 ng/ml or ≤ 4.88 ng/ml. Log-rank p<0.001.

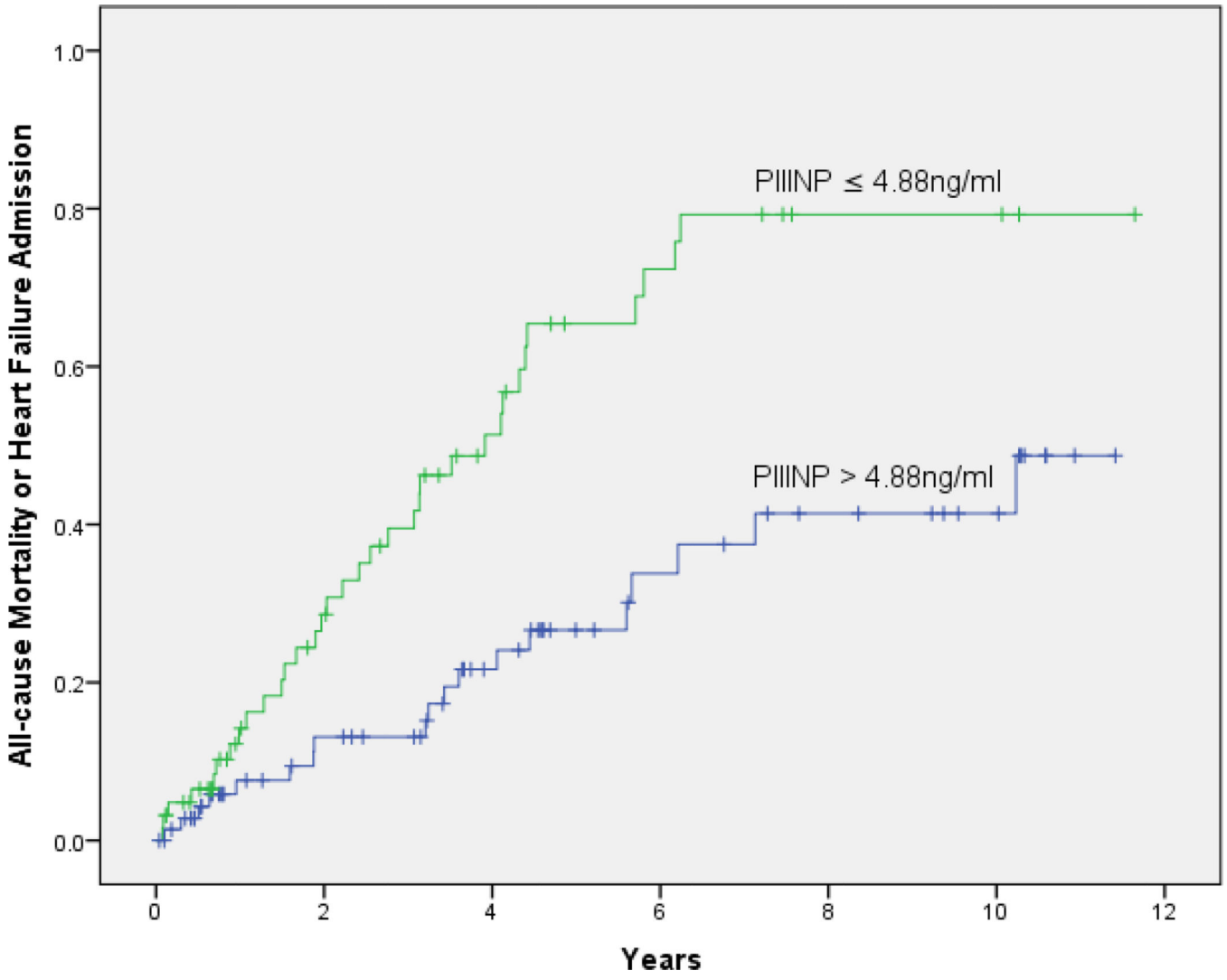

Figure 4.

Kaplan-Meier curves of all-cause mortality or heart failure hospitalization for patients stratified by procollagen type III N-terminal peptide (PIIINP) >4.88ng/ml or ≤4.88 ng/ml. Log-rank p=0.017.

Table 1

Baseline characteristics by PIIINP level

Characteristic	Serum PIIINP level		
	≤4.88ng/ml n= 75	>4.88ng/ml n=63	*p* Value
Age (years)	55 ± 15	59 ± 14	0.094
Male sex	33 (44)	28 (44)	1.000
BMI (kg/m^2)	35 ± 11	34 ± 12	0.877
Diabetes	22 (29)	21 (33)	0.713
Hypertension	61 (81)	52 (83)	1.000
Dyslipidemia	43 (57)	35 (56)	0.864
Atrial fibrillation/flutter	11 (15)	18 (29)	0.059
Ischemic heart disease	10 (13)	19 (30)	0.035
Tobacco use	42 (57)	32 (51)	0.497
Medication use			
ACE inhibitor or ARB	69 (93)	58 (92)	1.000
β-blocker	74 (100)	59 (94)	0.042
Hydralazine plus nitrate	8 (11)	13 (21)	0.156
Loop diuretic	54 (75)	54 (86)	0.136
Digoxin	19 (26)	17 (27)	0.999
Statin	44 (64)	35 (71)	0.431
NYHA functional class			
Class I	22 (30)	10 (16)	
Class II	24 (32)	20 (32)	0.110
Class III	28 (38)	33 (52)	
Blood pressure (mmHg)			
Systolic	127 ± 23	130 ± 26	0.557
Diastolic	73 ± 12	74 ± 16	0.700
Heart rate (bpm)	74 ±13	73 ± 14	0.697
S3 (%)	0	2 (3)	0.207
JVD, above 8 cm	2 (3)	5 (8)	0.246
Rales	0	4 (6)	0.041
Glomerular filtration rate	76 ± 25	60 ± 30	0.002
Mean LVEF	38 ± 13	33 ± 13	0.032
LVEF <40%	36 (52)	38 (68)	0.100

Mean ± SD or No (%)

*Extended release formulation doses shown

BMI, body mass index; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; bpm, beat per minute; S3, the third heart sound; JVD, jugular venous distension; PIIINP, procollagen type III N-terminal peptide; LVEF, left ventricular ejection fraction

Table 2

Unadjusted hazard ratios for all-cause mortality and hospitalization for heart failure associated with PIIINP levels and clinical characteristics

	All-cause Mortality			Mortality or Heart Failure Hospitalization		
Variable	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
PIIINP >4.88 ng/ml	4.93	2.21–11.02	<0.001	2.62	1.62–5.03	<0.001
PIIINP values	1.22	1.11–1.33	<0.001	1.19	1.04–1.28	<0.001
LVEF	0.96	0.91–0.99	0.014	0.98	0.96–1.04	0.106
Age	1.03	1.01–1.05	<0.001	1.02	1.01–1.04	0.018
Male	2.02	0.97–4.12	0.055	1.72	0.99–2.97	0.054
NYHA class II	1.90	0.70–5.16	0.206	2.26	0.98–5.2	0.055
NYHA class III	1.58	0.61–4.08	0.344	2.13	0.97–4.70	0.061
Ischemic heart disease	3.51	1.73–7.11	<0.001	1.49	0.82–2.69	0.187
Atrial fibrillation/flutter	3.54	1.68–7.48	<0.001	2.49	1.37–4.52	0.003
Glomerular filtration rate	0.976	0.96–0.99	0.003	0.98	0.97–0.99	<0.001
Diabetes Mellitus	1.66	0.80–3.45	0.175	1.69	0.96–2.97	0.069
Use of β-blocker	0.23	0.07–0.77	0.017	0.25	0.09–0.67	0.008

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PIIINP, procollagen type III N-terminal peptide

Table 3

Adjusted hazards ratios for all-cause mortality and hospitalization for heart failure

	All-cause Mortality			Mortality or Heart Failure Hospitalization		
Variable	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
PIIINP level >4.88 ng/ml	5.76	1.91–17.32	0.002	2.35	1.17–4.70	0.016
PIIINP level (continuous)*	1.19	1.04–1.36	0.010	1.12	1.01–1.23	0.024
LVEF	0.94	0.91–0.99	0.009	0.99	0.96–1.02	0.427
Age	1.01	0.97–1.06	0.580	1.00	0.97–1.03	0.945
Male	0.72	0.27–1.94	0.511	1.66	0.84–3.28	0.144
NYHA functional class II	1.04	0.30–3.59	0.946	2.23	0.81–6.13	0.122
NYHA functional class III	1.33	0.40–4.52	0.641	1.96	0.76–5.09	0.165
Ischemic heart disease	3.29	1.02–10.60	0.046	0.93	0.42–2.10	0.866
Atrial fibrillation/flutter	3.16	1.07–9.37	0.038	1.34	0.62–2.90	0.463
Glomerular filtration rate	1.43	0.50–4.11	0.504	0.98	0.97–0.99	0.018
Use of β-blocker	0.88	0.15–5.31	0.887	1.10	0.24–5.16	0.903

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PIIINP, procollagen type III N-terminal peptide;

*PIIINP was used as a continuous variable, and values were derived from a separate multivariate model that included all variables in the table.