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Clinical and Serum-Based Markers Are Associated with Death within 1 year of *de novo* Implant in Primary Prevention ICD Recipients

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Abstract

Background—Implantable cardioverter defibrillator (ICD) implantation is contraindicated in those with <1 year life expectancy.

Objective—To develop a risk prediction score for 1-year mortality in patients with primary prevention ICDs and to determine the incremental improvement in discrimination when incorporating serum-based biomarkers to traditional clinical variables.

Methods—We analyzed data from the PROSE-ICD study, a large prospective observational study of patients undergoing primary prevention ICD implantation who were extensively phenotyped for clinical and serum markers. We identified variables predicting 1-year mortality and synthesized them into a comprehensive risk scoring construct using backward selection.

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Results—Among 1,189 patients deemed by their treating physicians as having reasonable 1 year life expectancy, 62 patients died within 1 year of ICD implantation. The risk score, comprised of 6 clinical factors (age ≥ 75 years, New York Heart Association class III/IV, atrial fibrillation, eGFR <30mL/min/1.73m², diabetes, and use of diuretics), had good discrimination (AUC=0.77) for 1-year mortality. Addition of 3 biomarkers (TNF-αRII, pro-BNP, and cTnT) further improved model discrimination to 0.82. Patients with 0-1, 2-3, 4-6, or 7-9 risk factors had 1-year mortality rates of 0.8%, 2.7%, 16.1% and 46.2%, respectively.

Conclusions—Individuals with more co-morbidities and elevations of specific serum biomarkers were at increased risk for all-cause mortality despite being deemed as having reasonable 1 year life expectancy. A simple risk score comprised of readily available clinical data and serum biomarkers may better identify patients at high risk of early mortality and improve patient selection and counseling for primary prevention ICD therapy.

Keywords

sudden cardiac death; implantable cardioverter defibrillator; early mortality; ICD shock; primary prevention

INTRODUCTION

Implantable cardioverter defibrillators (ICDs) reduce all-cause mortality in patients with severe systolic heart failure.¹⁻⁴ However, these studies demonstrate that the benefit is only evident >1 year after ICD implantation. Hence, current guidelines recommend against ICD implantation among individuals who do not have a reasonable life expectancy of more than one year.⁵⁻⁶ In the selection of candidates for primary prevention ICD implantation, there are some patients who most clinicians would agree have a limited likelihood of meaningful survival (e.g., metastatic cancer). But in the majority of patients, the answer is less clear. We and others have made efforts to predict the risk for 1 year mortality in ICD recipients,⁷⁻¹⁵ but many of these studies have limited discrimination, analyses restricted only to clinical demographic variables, lack information regarding the delivery of appropriate ICD therapy prior to death and limited reporting on the mode of patient death.

Using data from the Prospective Observational Study of Implantable Cardioverter-Defibrillators (PROSE-ICD), a large prospective cohort of well phenotyped patients with ischemic and non-ischemic cardiomyopathy undergoing ICD implantation for primary prevention of sudden cardiac death (SCD), we sought to improve discrimination of individuals more likely to die within 1 year of ICD implantation by developing a clinical risk prediction score that incorporated readily available clinical risk factors and serum markers of inflammation, heart failure status, and cardiac injury.

METHODS

Study Design and Population

PROSE-ICD is a multicenter prospective cohort study of extensively phenotyped patients with systolic heart failure undergoing primary prevention ICD implantation who are deemed to have reasonable 1 year life expectancy. Details of the study design have been described

previously.¹⁶ Briefly, patients between 18-80 years of age referred for primary prevention ICD implantation were enrolled if they met any of the following criteria: (1) ischemic cardiomyopathy (myocardial infarction greater than 40 days prior to implant) with an ejection fraction of <30% and stable New York Heart Association (NYHA) Class I-III heart failure; (2) ischemic or non-ischemic cardiomyopathy with an ejection fraction <35% and NYHA Class II or III heart failure; or (3) patients with NYHA Class IV heart failure symptoms undergoing implantation of a cardiac resynchronization therapy (CRT) device with an ICD. Our study complies with the Declaration of Helsinki, and all 1,189 participants (867 men, 322 women) enrolled provided signed informed consent approved by their respective institutional review boards.

Clinical Data Collection

At enrollment and prior to ICD implantation, all patients underwent a comprehensive review of medical history and cardiovascular examination along with a digitally-recorded resting 12-lead electrocardiogram (ECG), a 5-min three-lead ECG, an echocardiogram (if one was not previously available) and blood serum collection. Medical history included data on New York Heart Association (NYHA) class, angina class, atrial fibrillation, smoking, diabetes, hypertension, other comorbidities, and medication use. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

The inflammatory biomarkers included C-reactive protein (CRP), interleukin-6 (IL-6), IL-10, and tumor necrosis factor receptor II (TNF- α RII). IL-6 (R&D Systems, Minneapolis MN), IL-10 (R&D Systems) and CRP (ALPCO Diagnostics, Salem NH) were measured with high-sensitivity ELISAs according to manufacturer's instructions. The lower limits of detection (LLOD) for CRP, IL-6, and IL-10 were 0.5 ng/ml, 0.036 pg/ml, and <0.5 pg/ml, respectively, with inter-assay coefficients of variation (CV) of 2.2%, 5%, and 6.3%, respectively. Soluble TNF- α RII is more stable than TNF- α and was measured to index levels of the cytokine using an ELISA (R&D Systems) with a LLOD of 0.6 pg/ml and inter-assay CV of 5.9%. The neurohumoral/cardiac injury biomarkers included pro-brain natriuretic peptide (pro-BNP), cardiac troponin T (cTnT), cardiac troponin I (cTnI), myoglobin, and creatine kinase MB (CK-MB). Pro-BNP was measured using an ELISA (ALPCO Diagnostics) with a LLOD of 5 fmol/ml and an inter-assay CV of 5.25%. CK-MB, myoglobin, cTnI and cTnT were measured using antibody-based electrochemiluminescence detection and patterned array sandwich ELISA (Meso Scale Discovery, Rockville MD). CK-MB, myoglobin and cTnI were measured in a multiplex format and cTnT in a monoplex format with LLODs of 0.021 ng/ml, 0.075 ng/ml, 1.24ng/ml and 0.72 pg/ml, respectively. The intra- and inter-assay CVs for the cardiac injury panels varied from 2.4-8.4% (mean 5.6%) and 4.3-9.5% (mean 7.8%), respectively.

Follow-up and Outcomes

Patients were evaluated every 6 months after ICD implantation either in person or by phone and soon after any ICD therapy recognized by the patient. For the current analysis, participants were followed for events through July 1, 2013. The primary endpoint of the study was mortality during the first year of ICD implantation. Deaths were ascertained by

phone contact with the next of kin and by searches of the National Death Index. Next of kin interviews regarding the circumstances surrounding the death, death certificates, and medical documentation around the time of death including ICD interrogations whenever possible were collected. This information was subsequently reviewed and adjudicated by two independent cardiologists. Each death event is adjudicated based on modified Hinkle-Thaler criteria. Appropriate ICD shock was defined as an ICD shock for adjudicated ventricular tachyarrhythmias. Arrhythmic events were adjudicated by two clinical cardiac electrophysiologists blinded to patient demographic information. Disagreements were reconciled by a third electrophysiologist.

Statistical Analyses

We used the logistic regression to assess the association between risk factors and all-cause mortality during the first year of ICD implantation. We performed a risk score development process by first utilizing readily available demographic and clinical risk factors only. All clinical variables associated with 1-year mortality with a p-value <0.2 in the univariate analysis were selected and entered into multivariable logistic regression for backward selection, where risk factors with p>0.05 were then removed from the model. All risk factors that remained statistically significant after backward selection were then incorporated into the “clinical” risk score. To generate a simple point scoring system, we assigned each variable a value of 0 if absent and a value of 1 if present. The total clinical score for each participant was then calculated by adding all the variables together.

To describe the predictive power of serum-based biomarkers of inflammation, heart failure status, and cardiac injury on 1 year mortality and assess whether they incrementally improved a “clinical” only risk score, we performed logistic regression of each biomarker on 1-year mortality adjusting for the risk factors included in the clinical score. Serum biomarkers that were independently associated with 1-year mortality were then incorporated into the clinical score to form a comprehensive clinical and serum biomarker risk score. Model discrimination was determined by the area under the receiver operating characteristic (ROC) curve (AUC), and risk reclassification was assessed using both net reclassification improvement (NRI) and integrated discrimination improvement (IDI). Confidence intervals for these statistics were obtained using boot-strapping. In addition, sensitivity analysis weighing each risk factor by their β -coefficients was performed and yielded virtually the same results (data not shown). All analyses were performed using STATA version 12 (StataCorp LP, College Station, Texas).

RESULTS

Among 1,189 individuals deemed to have reasonable 1 year life expectancy, a total of 62 (5.2%) patients died during the first year of ICD implantation; 59 (95%) without experiencing an appropriate ICD shock. Thirty-five (56.5%) of these deaths were attributed to a cardiac cause, primarily pump failure (n = 24) (**Table 1**). The median time to death in the early mortality group was 196 days (inter-quartile range 98 to 287 days). The average age of all study participants at baseline was 60.6 years (SD 12.7 years) (**Table 2**). Males comprised 72.9% of all subjects and 57.1% were white. Patients who died were on average

older (65.0 vs. 60.4 years), more likely to have NYHA class III/IV (62.9% vs. 38.1%), atrial fibrillation (50.0% vs. 24.9%), diabetes (54.8% vs. 33.7%), hypertension (77.4% vs. 62.0%), eGFR<30 mL/min/1.73 m² (22.6% vs. 3.9%), and to be treated with Thiazide/loop diuretics (88.7% vs. 71.2) and Warfarin (46.8% vs. 29.5%) (**Table 2**). After backward selection, 6 risk factors remained significantly associated with increased risk of 1-year mortality and composed the initial clinical risk score: age ≥ 75 years, NYHA class III/IV, atrial fibrillation, diabetes, eGFR <30 mL/min/1.73 m², and use of Thiazide/loop diuretics (**Table 3**). The AUC of the clinical score in predicting 1-year mortality was 0.77 (95% CI 0.70 to 0.84).

In univariate analysis, patients who died in the first year of ICD implantation had higher baseline levels of hs-CRP, IL-6, IL-10, TNF-αRII, pro-BNP, and cTnT (**Table 4**). In multivariate logistic regressions, TNF-αRII, pro-BNP, and cTnT remained independently associated with 1-year mortality after adjusting for risk factors included in the clinical score (**Table 5**). Adding baseline serum biomarkers (e.g., TNF-αRII, pro-BNP, and cTnT) to the clinical score significantly improved the AUC for prediction of 1-year mortality to 0.82 (95% CI 0.76 to 0.88). Improvement in discrimination was also confirmed by the IDI (0.04; 95% CI, 0.01 to 0.07), suggesting further separation of events from non-events by incorporating biomarkers in the risk prediction. A net 59.5% of the patients without events were reclassified into lower risk, and a net 17.6% of the patients with events were reclassified into higher risk, resulting in a total continuous NRI of 77.2%. Patients with a comprehensive clinical and serum biomarker score of 0-1 (35.7%), 2-3 (47.2%), 4-6 (16.0%), or 7-9 (1.2%) had a 1-year mortality rate of 0.8%, 2.7%, 16.1%, and 46.2%, respectively (**Figure 1**).

DISCUSSION

In a prospective cohort of patients undergoing ICD implantation for primary prevention of SCD who were deemed by current clinical practice to have reasonable 1 year life expectancy, 5.2% of the patients died within the first year of ICD implantation. A simple risk score based on 6 readily available clinical variables (age ≥ 75 years, NYHA class III/IV, atrial fibrillation, diabetes, eGFR<30 mL/min/1.73m², use of diuretics) was predictive of 1-year mortality after ICD implantation. The addition of 3 serum biomarkers (TNF-αRII, pro-BNP, and cTnT>90th percentile) to the clinical variables significantly improved risk prediction and may further aid in the identification of patients at high risk for early mortality despite appearing as having reasonable 1 year survival.

Several studies have explored risk prediction for 1-year mortality in ICD patients. Risk factors previously identified by multiple studies include advanced age,^{7-9, 11-12, 14, 17} reduced ejection fraction,^{7, 10, 12, 17} atrial fibrillation,^{7-9, 14} kidney dysfunction,^{7-8, 12-14, 17-18} NYHA class III/IV,⁸⁻⁹ diabetes,^{9, 17} and peripheral arterial disease.^{12, 17} Other risk factors identified by a single study include male gender,¹⁴ absence of beta-blocker¹⁰ or ACE-inhibitor use,¹¹ reduced quality of life,¹¹ underweight,⁹ low mean arterial pressure,⁹ valvular heart disease,¹⁴ organ dysfunction,¹³ and Charlson comorbidity index.¹⁵ However, the majority of the studies included both primary and secondary prevention patients, with the proportion of secondary prevention patients ranging from 25% to 100%. Hence, risk prediction derived from these studies may not apply to patients being

considered for primary prevention ICDs. Additionally, many of these studies have limited discrimination, restricted the analysis to clinical demographics only or had no information on whether ICD therapy was received prior to death. These are important considerations especially when applying such a tool in management decisions related to primary prevention ICD utilization.

Currently, there has been only one risk prediction model for 1-year mortality that was developed exclusively in primary prevention patients.⁷ This study reported a 1-year mortality rate of 4.8% and a final risk score based on age ≥ 75 years, ejection fraction $\leq 20\%$, atrial fibrillation, and eGFR ≤ 30 mL/min/1.73m².⁷ However, serum biomarkers of inflammation, heart failure status, and cardiac injury were not measured in this study, and causes of death were not reported. Our study found a comparable 1-year mortality rate of 5.2%, and identified a similar set of clinical predictors. In addition, we found that serum biomarkers including TNF- α RII, pro-BNP, and cTnT were also independently associated with 1-year mortality, and the addition of these biomarkers to the clinical model further improved risk prediction. The improvement in prediction performance was mainly attributed to the improvement in the identification of patients with low 1-year mortality risk (i.e., 59.6% of the patients without events were correctly reclassified into a lower risk). In addition, we found that only 3 early-mortality patients received an appropriate ICD shock prior to death, suggesting that the majority of the patients who died early after ICD implantation did so without the benefit of device therapy and died from causes unrelated to ventricular tachyarrhythmias. Indeed, 22.6% of the 1-year deaths in our study were due to a non-cardiac cause and 56.5% were due to a cardiac cause. Among those who died from a cardiac cause, 68.6% were attributed to pump failure.

Inflammation plays a key role in the pathogenesis of heart failure. High levels of TNF- α and its receptor have been associated with heart failure progression and mortality in patient with both preserved and reduced ejection fraction.¹⁹⁻²² Pro-BNP, a neurohumoral marker of myocyte stress in response to myocardial tension and increased intravascular volume, has also been consistently shown to predict poor outcome including mortality among heart failure patients.²²⁻²³ Similarly, markers of myocardial damage including cTnT predict major cardiovascular events and all-cause mortality in heart failure patients.^{21-22, 24} Recent studies with high-sensitivity troponin have further found that cTnT is an independent predictor not only for cardiac mortality, but also for non-cardiac mortality.²⁵ Our findings demonstrate that more than half of the deaths in the first year after ICD implantation were due to a cardiac cause, primarily pump failure. Findings from our study suggest that inflammation, neurohumoral modulation, and cardiac injury may be associated with the progression of heart failure and can improve risk prediction for early mortality beyond traditional clinical risk factors. Hence, obtaining information on these serum biomarkers at the time of ICD implantation may significantly improve discriminatory power for early mortality.

Current guidelines recommend against ICD implantation among individuals who do not have a “reasonable expectation of survival with a good functional status for more than 1 year” and emphasize the integration of factors in decision-making.⁵⁻⁶ However, it is currently left to physician judgment as to whether an individual has reasonable survival expectations within 1 year of implant. Except for a few conditions (e.g., metastatic end-stage

cancer), there is little consensus on what constitutes higher risk. Our study, consisting of patients deemed to have reasonable 1 year survival, has identified several readily available clinical and serum-based predictors that may provide the basis for a more refined risk stratification strategy. Results from our study show that while subjective risk stratification has some utility (i.e., only 5.2% died), it can be improved upon through the use of this simple risk score assessment. In fact, the risk of 1-year mortality increased to >10% among patients who had 4-6 risk factors, and further increased to >40% among those who had 7 or more risk factors. These findings may allow for more informed patient counseling and decision-making regarding the potential risks and benefits of primary prevention ICD implantation, particularly among those who have >4 risk factors. However, due to the limited number of patients with 7 or more risk factors, these results will need to be further validated and confirmed prospectively in larger samples before attempting to exclude individuals from ICD therapy.

A few limitations of this study need to be considered. The number of deaths that occurred in the first year was relatively small and may limit our ability to produce stable estimates and identify additional risk markers that may also have impact. The small number of deaths also prohibited us from categorizing each risk predictor into more granular groups to further weigh in the extent of abnormality. The mode of death could not be firmly established in many patients due to the lack of reliable records when patients died out of hospital. As a consequence, we could not examine differences in the cause-specific mortality or whether different predictors may have different impact on cardiac vs. non-cardiac mode of death. The selection of predictors was based on all available information collected at the study enrollment. Although we measured a comprehensive list of markers that were most likely to be encountered in clinical practice, it is possible that unmeasured predictors (especially those more recently identified) may have been missed. In addition, our risk score was not validated in a separate cohort. We elected not to divide the study population into a derivation and a validation cohort due to the small number of events. However, the clinical risk predictors identified in our analysis were consistent with previous studies supporting the validity of our findings. The current study focused on enrollment of individuals with evidence of systolic heart failure. Therefore, findings from this study may not apply to the smaller group of individuals with preserved systolic function undergoing primary prevention ICD implantation such as long QT syndrome and other inherited channelopathies. These latter types of individuals likely have even lower risk for early mortality and may not need additional more refined risk stratification since they often lack potentially life-threatening co-morbidities that are often associated with systolic dysfunction.

CONCLUSIONS

In this large prospective study of patients undergoing primary prevention ICD implantation who were deemed to have reasonable 1 year life expectancy, a simple risk score incorporating clinical and serum biomarker information was able to identify patients with a high risk of 1-year mortality after *de novo* ICD implantation. Findings from the current analysis may provide a basis for identifying individuals who are at high risk for early death despite being clinically judged to have reasonable 1 year survival.

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ABBREVIATIONS

ICD	implantable cardioverter defibrillator
SCD	sudden cardiac death
NYHA	New York Heart Association
CRT	cardiac resynchronization therapy
ECG	electrocardiogram
CRP	C-reactive protein
IL	interleukin
TNF	tumor necrosis factor
BNP	brain natriuretic peptide
TnT	troponin T
ROC	receiver operating characteristic curve
AUC	area under the curve

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Clinical Perspectives

Current guidelines recommend against ICD implantation among individuals who do not have a reasonable life expectancy of more than one year. However, except for a few conditions (e.g., metastatic end-stage cancer), current practice relies on clinical judgment which is often subjective and variable. Our analysis of a large prospective study of patients deemed to have reasonable 1 year survival and undergoing primary prevention ICD implantation showed that a simple risk score comprised of 6 readily available clinical markers (age ≥ 75 years, New York Heart Association [NYHA] class III/IV, atrial fibrillation, eGFR <30 mL/min/1.73m², diabetes, and use of diuretics) identified patients at high risk of 1-year mortality after *de novo* ICD implantation. Addition of 3 biomarkers (TNF- α RII, pro-BNP, and cTnT) further improved model discrimination. Patients with 0-1, 2-3, 4-6, or 7-9 risk factors had 1-year mortality rates of 0.8%, 2.7%, 16.1% and 46.2%, respectively. Results from the current analysis may provide the basis for a more refined risk stratification strategy to identify individuals who are at high risk of early mortality and unlikely to benefit from the ICDs, among those who are otherwise deemed to have reasonable 1 year survival. These findings may also allow for a more informed patient counseling and decision-making particularly among patients presenting with >4 risk factors.

Figure 1. Distribution of the clinical and biomarker risk score (A), and the Kaplan-Meier survival curves by risk score categories (B).

Table 1

Causes of 1-year mortality in patients with primary prevention ICDs

Causes of death	Number of deaths (%)
Cardiac	35 (56.5)
Pump failure	24 (38.7)
Lethal VT/VF	6 (9.7)
Asystole	1 (1.6)
Non-cardiac	14 (22.6)
Respiratory failure	5 (8.1)
Septic shock	8 (12.9)
Other	2 (3.2)
Undetermined	3 (4.8)
Undetermined	13 (21.0)
Total	62 (100)

Table 2Baseline characteristics of participants, by 1-year mortality^{*}

Characteristic	Total (n = 1189)	Alive (n = 1127)	Dead (n = 62)	p-value
Age (year)	60.6 ± 12.7	60.4 ± 12.6	65.0 ± 12.9	0.005
Sex				0.09
Male	867 (72.9)	816 (72.4)	51 (82.3)	
Female	322 (27.1)	311 (27.6)	11 (17.7)	
Race				0.19
White	679 (57.1)	650 (57.7)	29 (46.8)	
Black	477 (40.1)	447 (39.7)	30 (48.4)	
Other	33 (2.8)	30 (2.7)	3 (4.8)	
Smoking				0.95
Never	398 (33.5)	377 (33.5)	21 (33.9)	
Former	541 (45.5)	512 (45.4)	29 (46.8)	
Current	250 (21.0)	238 (21.1)	12 (19.4)	
Body mass index (kg/m ²)	29.8 ± 6.5	29.7 ± 6.6	30.0 ± 5.9	0.77
Ejection fraction (%)	22.3 ± 7.4	22.3 ± 7.3	20.8 ± 8.4	0.12
NYHA class				<0.001
Class I	196 (16.5)	195 (17.3)	1 (1.6)	
Class II	524 (44.1)	502 (44.5)	22 (35.5)	
Class III	464 (39.0)	425 (37.7)	39 (62.9)	
Class IV	5 (0.4)	5 (0.4)	0 (0.0)	
Cardiomyopathy				0.24
Non-ischemic	547 (46.0)	523 (46.4)	24 (38.7)	
Ischemic	642 (54.0)	604 (53.6)	38 (61.3)	
Atrial fibrillation	312 (26.2)	281 (24.9)	31 (50.0)	<0.001
Diabetes	414 (34.8)	380 (33.7)	34 (54.8)	0.001
Hypertension	747 (62.8)	699 (62.0)	48 (77.4)	0.02
eGFR (mL/min/1.73 m ²)				<0.001
90	278 (23.4)	272 (24.1)	6 (9.7)	
60-89	542 (45.6)	526 (46.7)	16 (25.8)	
30-59	302 (25.4)	276 (24.5)	26 (41.9)	
<30	58 (4.9)	44 (3.9)	14 (22.6)	
QTc (msec)	459.8 ± 43.4	459.2 ± 43.4	470.3 ± 43.0	0.05
QRS duration (msec)	118.7 ± 30.7	118.3 ± 30.7	125.8 ± 29.8	0.06
Device type				
ICD	866 (72.8)	827 (73.4)	39 (62.9)	0.07
CRT-D	323 (27.2)	300 (26.6)	23 (37.1)	
Medications				
ACE-I/ARB	850 (71.5)	807 (71.6)	43 (69.4)	0.70
Beta blocker	1061 (89.2)	1007 (89.4)	54 (87.1)	0.58

Characteristic	Total (n = 1189)	Alive (n = 1127)	Dead (n = 62)	p-value
Thiazide/loop diuretics	857 (72.1)	802 (71.2)	55 (88.7)	0.003
Aldosterone antagonist	302 (25.4)	288 (25.6)	14 (22.6)	0.60
ASA	781 (65.7)	740 (65.7)	41 (66.1)	0.94
Warfarin	361 (30.4)	332 (29.5)	29 (46.8)	0.004
Clopidogrel	295 (24.8)	281 (24.9)	14 (22.6)	0.68
Digitoxin/digitalis	284 (23.9)	265 (23.5)	19 (30.6)	0.20
Statin	823 (69.2)	781 (69.3)	42 (67.7)	0.80

* Values are numbers (%) or means $\pm$ SD.

Table 3Risk factors associated with 1-year mortality^{*}

	OR (95% CI)	p-value
Age ≥ 75 years	1.98 (1.02, 3.85)	0.04
NYHA III/IV	1.96 (1.13, 3.40)	0.017
Atrial fibrillation	2.51 (1.43, 4.38)	0.00
eGFR <30 mL/min/1.73 m ²	5.99 (2.92, 12.26)	<0.001
Diabetes	1.87 (1.07, 3.26)	0.028
Thiazide/loop diuretics	2.76 (1.21, 6.32)	0.02

^{*} Model included all variables in this table.

Table 4Baseline levels of biomarkers, by vital status at 1 year^{*}

Biomarkers	Total (n = 1189)	Alive (n = 1127)	Dead (n = 62)	p-value
hs-CRP (μg/mL)	4.4 (1.6, 10.6)	4.3 (1.6, 10.2)	11.6 (3.5, 16.7)	0.001
IL-6 (pg/mL)	2.0 (1.1, 4.3)	2.0 (1.1, 4.1)	4.2 (2.0, 7.8)	0.001
IL-10 (pg/mL)	1.4 (0.9, 2.8)	1.4 (0.9, 2.7)	1.8 (1.0, 4.6)	0.03
TNF-αRII (pg/mL)	3160 (2319, 4754)	3098 (2294, 4542)	4961 (3444, 8047)	<0.001
pro-BNP (ng/mL)	2.6 (1.7, 4.1)	2.5 (1.7, 3.9)	5.1 (2.7, 8.8)	<0.001
cTnT (ng/mL)	0.005 (0, 0.037)	0.004 (0, 0.034)	0.064 (0.021, 0.149)	<0.001
cTnI (ng/mL)	0.013 (0, 0.054)	0.013 (0, 0.052)	0.027 (0.004, 0.100)	0.09
CK-MB (ng/mL)	2.5 (1.7, 4.1)	2.5 (1.7, 4.1)	2.6 (1.6, 5.0)	0.64
Myoglobin (ng/mL)	20.3 (0, 24.3)	20.3 (0, 24.3)	20.4 (0, 26.1)	0.87

* Values are medians (inter-quartile range).

Table 5Odds ratio (95% CI) for 1-year mortality comparing biomarker levels >90th vs. 90th percentile^{*}

	OR (95% CI)[†]	p-value
hs-CRP	1.52 (0.64, 3.61)	0.35
IL-6	1.56 (0.69, 3.51)	0.28
IL-10	1.08 (0.47, 2.49)	0.86
TNF-αRII	2.55 (1.07, 6.12)	0.04
pro-BNP	2.44 (1.13, 5.30)	0.02
cTnT	3.90 (1.96, 7.76)	<0.001
cTnI	1.59 (0.65, 3.88)	0.31
CK-MB	1.16 (0.45, 3.02)	0.76
Myoglobin	1.53 (0.65, 3.58)	0.33

^{*}The 90th percentiles of TNF-αRII, pro-BNP, and cTnT were 6760 pg/mL, 7.2 ng/mL, and 0.105 ng/mL, respectively.

[†]Model adjusted for age (<75, 75), eGFR (<30, 30), diabetes, use of diuretics, NYHA (I/II, III/IV), and atrial fibrillation.