

Assessment of a multi-marker risk score for predicting cause-specific mortality at three years in older patients with heart failure and reduced ejection fraction

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Abstract

Background: *Due to increasing co-morbidity associated with aging, heart failure (HF) has become more prevalent and heterogeneous in older individuals, and non-cardiovascular (CV) mortality has increased. Previously, we defined a multi-marker modality that included cystatin C (CysC), troponin T (TnT), and age. Here, we validated this multi-marker risk score by evaluating its predictions of all-cause mortality and CV mortality in an independent population of older individuals with HF and reduced ejection fraction (HFrEF).*

Methods: *This prospective cohort study included 124 patients, median age 73 years, that had HFrEF. We determined all-cause mortality and CV mortality at a 3-year follow-up. We compared the risk score to the N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) for predicting all-cause mortality and CV mortality.*

Results: *High risk scores were associated with both all-cause mortality (HR 4.2, 95% CI 2.2–8.1, $p < 0.001$) and CV mortality (HR 3.6, 95% CI 1.7–8.0, $p = 0.0015$). Receiver operating characteristics showed similar efficacy for the risk score and NT-proBNP in predicting all-cause mortality (HR 0.74, 95% CI 0.65–0.81 vs. HR 0.74, 95% CI 0.65–0.81, $p = 0.99$) and CV mortality (HR 0.68, 95% CI 0.59–0.76 vs. HR 0.67, 95% CI 0.58–0.75, $p = 0.95$). When the risk score was added to the NT-proBNP, the continuous net reclassification improvement was 56% for predicting all-cause mortality (95% CI 18–95%, $p = 0.004$) and 45% for predicting CV mortality (95% CI 2–89%, $p = 0.040$).*

Conclusions: *In HFrEF, a risk score that included age, TnT, and CysC showed efficacy similar to the NT-proBNP for predicting all-cause mortality and CV mortality in an older population. (Cardiol J 2015; 22, 1: 31–36)*

Key words: heart failure, prognosis, cardiovascular mortality, biomarkers, risk score

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Introduction

Approximately 1–2% of the population in the western world has heart failure (HF) [1]. The prevalence of HF exceeds 8% among individuals over 75 years old [1]. The annual mortality varies from 5% [2] to 75% in cases of end-stage HF [3]. This broad range indicates that the prognosis is extremely diverse and can be difficult to assess in individual patients. In older patients with HF that have a reduced ejection fraction (HFrEF), about two thirds of deaths have been attributed to cardiovascular (CV) causes [4]. Therefore, approximately one third of deaths are due to non-CV causes. These latter causes are probably related to the increasing rate of co-morbidity; thus, HF appears to be heterogeneous in older individuals.

We previously developed a prognostic model that aimed to account for individual variations and confounding factors due to comorbidity in older individuals. This model comprised 3 risk markers that were highly associated with all-cause mortality [5]. The model produced a risk score that reflected the severity of the 3 risk markers: age, serum troponin T (TnT), and serum cystatin C (CysC) [5]. Each risk marker defined as age > 75 years, TnT > 10 ng/L and CysC > 1.3 mg/L adds 1 point respectively in the risk score with total score levels ranging from 0 (lowest risk) to 3 points (highest risk).

The present study aimed to evaluate this risk score in a validation cohort of older patients with HFrEF.

Methods

Study cohort and diagnosis

This prospective study included patients scheduled to undergo echocardiography at the Department of Clinical Physiology, Sahlgrenska University Hospital, Gothenburg, Sweden, in 2010. Eligible patients had a final diagnosis of HFrEF based on HF symptoms and a left ventricular ejection fraction (LVEF) < 50% [6]. Two patients were excluded from the study due to the lack of a Swedish identification number, which would make any follow-up impossible.

All patients underwent echocardiography, blood sampling, and a clinical examination within approximately 24 h after echocardiography. Echocardiograms were analyzed by an echocardiography specialist, independent of the study investigators, who was blinded to other variables in this study.

The study protocol was approved by the Ethics Committee at the University of Gothenburg.

Written informed consent was obtained from all the patients and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Laboratory analyses

The N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), CysC, high-sensitivity-TnT and creatinine measurements were obtained from the routine laboratory services provided by the Clinical Chemistry Laboratory at Sahlgrenska University Hospital. The estimated glomerular filtration rate was calculated according to the Cockcroft-Gault formula. The performance of the laboratory assays was described previously [7, 8].

Follow-up and outcomes

All patients were followed up at 3 years. Data on the causes of death were obtained from the death registry of the National Board of Health and Welfare in Sweden. Outcome measures were all-cause mortality and CV mortality. The causes of death were classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). The automatic coding of medical entities (ACME) system [9] was used to select the underlying cause of death. ACME used the ICD codes and their locations recorded on the death certificate for determining the cause of death. CV mortality was defined as an underlying cause of death that was classified as I05-I09 (chronic rheumatic heart diseases), I20-I51 (ischemic heart disease, pulmonary heart disease, diseases of pulmonary circulation, and other forms of heart disease), or I60-I69 (cerebrovascular diseases).

Statistical analyses

Kaplan-Meier analyses were used to evaluate possible associations between mortality and the risk scores. Hazard ratios (HR) with confidence intervals were calculated to evaluate risks. Univariate comparisons between dead and alive at 3 years were calculated with median tests. Dichotomous variables were analyzed with Monte-Carlo estimates. Receiver operating characteristic (ROC) curves were used to assess the prognostic properties of the risk score and the NT-proBNP classification. Areas under the ROC curves (AUC) were compared with the DeLong methodology [10]. Statistical analyses were performed with SPSS version 20 and Medcalc 12. All probabilities were 2-tailed, and p values < 0.05 were considered significant. NT-proBNP levels were classified based on 3 previously defined risk groups [5] (low risk

Table 1. Baseline characteristics of patients that survived or died at the 3-year follow-up.

Variable	Survived (n = 87)	Died (n = 37)	P
Clinical data			
Age	72 (63–78)	78 (71–84)	0.20
Gender — male	72%	73%	1.0
Systolic BP [mm Hg] (median + IQR)	125 (110–150)	125 (110–145)	0.88
Diastolic BP [mm Hg] (median + IQR)	75 (65–87)	70 (70–80)	0.70
Echocardiogram parameters			
LVEF [%]	35 (30–40)	33 (25–40)	0.86
LVDD [cm] (median + IQR)	6 (5–6)	6 (5–7)	0.98
PA [mm Hg] (median + IQR)	38 (30–45)	42 (30–50)	0.36
Stroke volume (median + IQR)	53 (44–65)	52 (41–59)	1.0
Cardiovascular risk factors			
Smoking	30%	35%	0.67
Hypertension	38%	35%	0.84
Diabetes mellitus	20%	35%	0.071
Cardiovascular disease			
Myocardial infarction	45%	43%	1.0
Angina pectoris	5.7%	8.1%	0.70
Atrial fibrillation	38%	35%	0.84
Comorbidity			
Pulmonary disease	21%	24%	0.81
Stroke	9.2%	22%	0.079
Renal failure (GFR < 60)	35%	73%	< 0.001
Medications			
ACE inhibitors	52%	32%	0.052
Beta-blockers	83%	70%	0.15
Diuretics	51%	84%	0.001
Laboratory markers			
S-creatinine [$\mu\text{mol/L}$] (median + IQR)	92 (74–106)	121 (89–176)	0.016
Estimated GFR [mL/min] (median + IQR)	75 (56–98)	43 (29–62)	0.001
Cystatin C [mg/L] (median + IQR)	1.0 (0.82–1.2)	1.7 (1.2–2.2)	< 0.001
High-sensitivity-troponin T [ng/L] (median + IQR)	24 (8–63)	49 (24–105)	0.016
NT-proBNP [ng/L] (median + IQR)	1670 (569–3410)	5890 (2200–20600)	0.016

ACE — angiotensin converting enzyme inhibitor; BP — blood pressure; GFR — glomerular filtration rate; IQR — interquartile range; LVDD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro B-type natriuretic peptide; PA — pulmonary artery

< 2000 ng/L, medium risk = 2000–8000 ng/L, and high risk \geq 8000 ng/L). Reclassification improvement was assessed with the continuous net reclassification improvement (NRI) method [11], because appropriate risk levels depend on the clinical situation and available resources. One patient (survivor at 3 years) was excluded from statistical analyses of laboratory data and the risk score due to the lack of available laboratory results.

Results

Baseline characteristics

The study participants comprised a representative population of individuals with HF_rEF. They had a median age of 73 years (interquartile range

64–80 years). Baseline characteristics for patients that had died or survived at the 3-year follow up are presented in Table 1.

All-cause and cardiovascular mortality

In this cohort, all-cause mortality was 30% and CV mortality was 21%. The risk score was able to separate individuals with low risk (0–1 score points) from those with moderate-high risk (2–3 score points) for all-cause mortality (HR 4.2, 95% confidence interval [CI] 2.2–8.1, $p < 0.001$, 0–1 vs. 2–3 score points; Fig. 1) and for CV mortality (HR 3.6, 95% CI 1.7–8.0, $p = 0.0015$, 0–1 vs. 2–3 score points; Fig. 2). The probabilities of survival for patients in the 3 different classes of NT-proBNP are presented in Figures 3 and 4 for comparison.

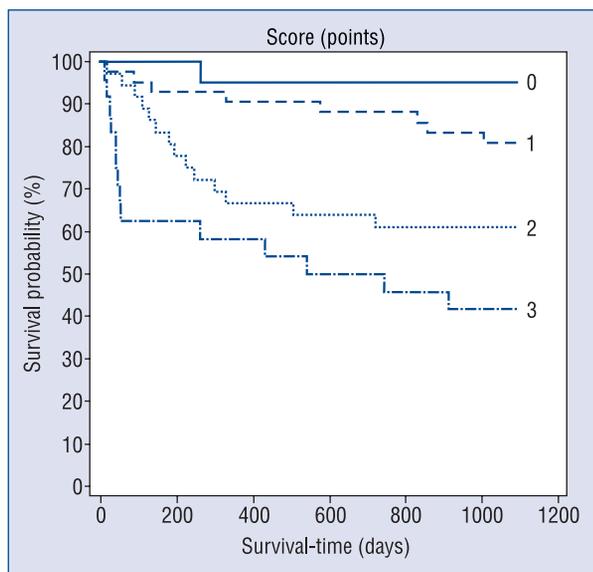


Figure 1. Association between the risk score and all-cause mortality. The risk score ranged from 0 to 3 points. The lines indicate the survival probability for individuals with the indicated scores, over the 3-year study period; $p < 0.001$ for comparison between individuals with 0–1 vs. 2–3 points.

There was no difference in the AUCs between the predictions assessed with the risk score and those assessed with the NT-proBNP for either all-cause mortality (HR 0.74, 95% CI 0.65–0.81 vs. HR 0.74, 95% CI 0.65–0.81, $p = 0.99$) or CV mortality (HR 0.68, 95% CI 0.59–0.76 vs. HR 0.67, 95% CI 0.58–0.75, $p = 0.95$). However, when the risk score was added to the NT-proBNP classification, the NRI for predicting all-cause mortality was 56% (95% CI 18–95%, $p = 0.004$) and the NRI for predicting CV mortality was 45% (95% CI 2–89%, $p = 0.040$).

Subgroup analyses of patients with NT-proBNP < 2500 ng/L and ≥ 2500 ng/L

The risk score was able to differentiate risk levels in a subgroup of patients with NT-proBNP < 2500 ng/L. Two groups were distinguished for all-cause mortality ($p < 0.046$; scores 0–1 vs. 2–3 points) and for CV mortality ($p = 0.040$; scores 0–1 vs. 2–3 points). In a subgroup of patients with NT-proBNP ≥ 2500 ng/L, the risk score also differentiated two risk groups for all-cause mortality ($p < 0.021$; scores 0–1 vs. 2–3 points), but not for CV mortality ($p = 0.13$; scores 0–1 vs. 2–3 points).

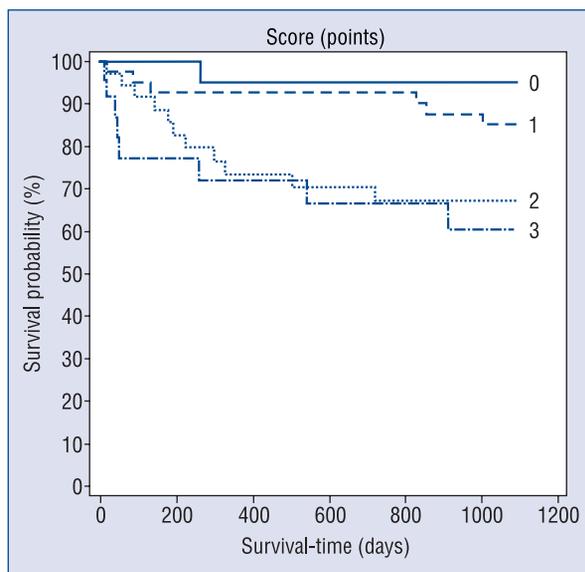


Figure 2. Association between the risk score and cardiovascular mortality. The risk score ranged from 0 to 3 points. The lines indicate the survival probability for individuals with the indicated scores, over the 3-year study period; $p = 0.0015$ for comparison between individuals with 0–1 vs. 2–3 points.

Discussion

This study examined a real-life cohort of older patients with HF to assess our previously developed multi-marker prognostic risk score, which included age, TnT, and CysC [5]. Our present results showed that the efficacy of our risk score was similar to that of the NT-proBNP classification for predicting all-cause mortality and CV mortality. Moreover, a combination of both the risk score and the NT-proBNP classification provided higher prognostic value than the NT-proBNP classification alone, for both all-cause and CV mortality.

In our cohort, approximately 70% of patients died from CV causes. This was consistent with results from previous studies. Henkel et al. [4] found that CV mortality constituted 64% of all deaths in a cohort aged 75.0 ± 12.7 years with HF rEF. Another study by Mehta et al. [11] showed that CV mortality constituted 86% of all deaths in a cohort aged 75.2 ± 12.4 years.

The present validation cohort was different from our previous HF cohort in 3 important aspects: (1) This study was conducted prospectively in patients scheduled to undergo echocardi-

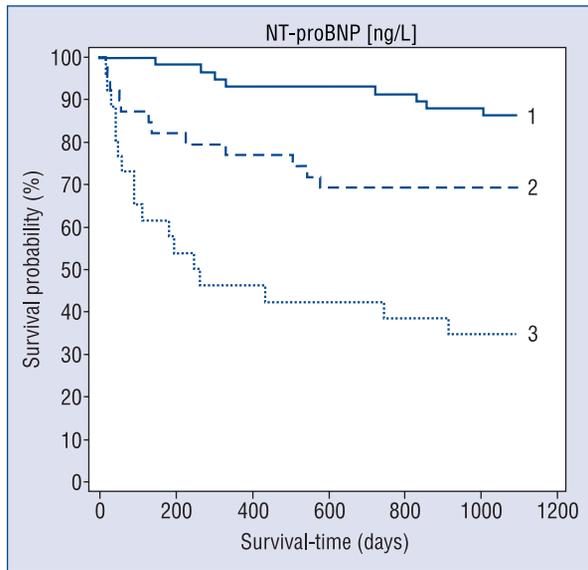


Figure 3. Association between different N-terminal pro B-type natriuretic peptide (NT-proBNP) risk levels (low risk < 2000 ng/L, medium risk = 2000–8000 ng/L, and high risk \geq 8000 ng/L) and all-cause mortality ($p < 0.001$).

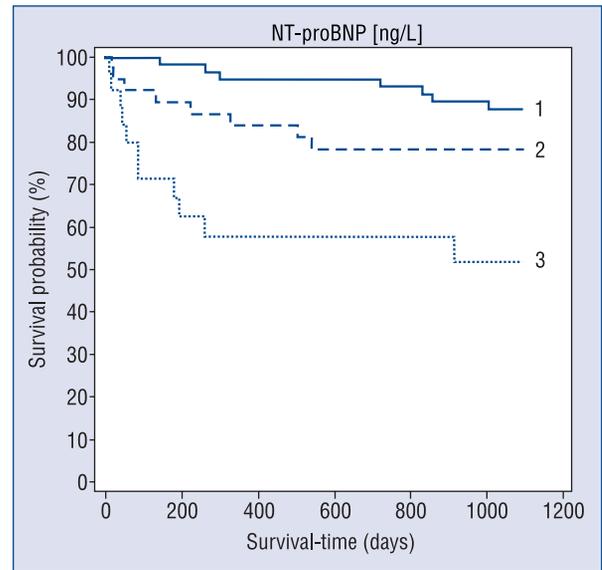


Figure 4. Association between different N-terminal pro B-type natriuretic peptide (NT-proBNP) risk levels (low risk < 2000 ng/L, medium risk = 2000–8000 ng/L, and high risk \geq 8000 ng/L) and cardiovascular mortality ($p < 0.001$).

graphy due to clinically suspected HF. Therefore, there was a short time delay between echocardiography and biomarker analyses; (2) Patients with LVEF \geq 50% were excluded in this validation cohort; (3) The present validation cohort consisted of patients referred to echocardiography both from the hospital and from primary care; in contrast, the score was previously developed with patients in hospital care. Despite these differences in cohorts, the risk score remained effective for predicting adverse outcomes.

Compared to the NT-proBNP classification, the score had several main advantages. (1) It provided complementary prognostic information to the NT-proBNP for predicting both all-cause and CV-mortality, as indicated by the NRI; (2) The risk score could stratify risk among patients with relatively low levels of NT-proBNP (< 2500 ng/L). Among this group of patients, the all-cause mortality was 35% different between patients with scores of 0–1 points vs. those with scores of 2–3 points (data not shown). Precise prognostic information is important for tailoring treatment to individual patients and/or for facilitating the allocation of limited health care resources; (3) It could be argued that the risk score may be less influenced than NT-proBNP levels by analytical and intra-individual variations [12, 13], which might compromise the

accuracy of prognostic assessments; (4) The risk score takes into account renal function and high-sensitivity TnT levels, both known markers of risk in HF. In fact, CysC has been shown to be a stronger predictor of mortality than creatinine in older patients with HF [14]. Moreover, de Antonio et al. [15] found that high-sensitivity TnT provided prognostic information in patients with HF with a median age of 70.3 years, even after adjustment for NT-proBNP and other risk factors.

Our proposed risk score is simpler to apply than, for instance, the Seattle Heart Failure Model [16] and the MAGGIC risk score [17]. This facility might encourage broader implementation, because busy clinicians must typically prioritize multiple tasks. Therefore, we anticipate that our suggested risk score may be a valuable tool in clinical practice in the future. However, one potential weakness in this study was a rather small sample size.

Conclusions

In HFREF, a risk score that included age, TnT, and CysC had an accuracy similar to that of the NT-proBNP classification for predicting both all-cause mortality and CV mortality. A combination of the NT-proBNP and the risk score provided high prognostic value for predicting both all-cause and CV mortality.

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Conflict of interest: None declared

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