

Assessment of a multimarker strategy for prediction of mortality in older heart failure patients: a cohort study

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ABSTRACT

Objective: Primarily to develop a multimarker score for prediction of 3-year mortality in older patients with decompensated heart failure (HF).

Design: Prospective cohort study.

Setting: Secondary care. Single centre.

Patients and biomarkers: 131 patients, aged ≥ 65 years, with decompensated HF were included. Assessment of biomarkers was performed at discharge.

Primary outcome measure: 3-year mortality.

Results: Mean age was 73 ± 11 years; mean left ventricular ejection fraction, $43 \pm 14\%$; 53% were male. The 3-year mortality was 53.4%. The following N-terminal brain natriuretic peptide (NTproBNP) levels could optimally stratify mortality: <2000 ng/l ($n=39$), 30.8% mortality; 2000–8000 ng/l ($n=58$), 51.7% mortality; and >8000 ng/l ($n=34$), 82.4% mortality. However, in the 2000–8000 ng/l range, NTproBNP levels had low-prognostic capacity, based on the area under the receiver operating characteristic curve (AUC=0.53; 95% CI 0.40 to 0.67). In this group, multivariate analysis identified age, cystatin C (CysC), and troponin T (TnT) levels as independent risk factors. A risk score based on these three risk factors separated a high-risk and low-risk groups within the NTproBNP range of 2000–8000 ng/l. The score exhibited a significantly higher AUC (0.75; 95% CI 0.62 to 0.86) than NTproBNP alone ($p=0.03$) in this NTproBNP group and had similar prognostic capacity as NTproBNP in patients below or above this NTproBNP range ($p=0.57$). Net reclassification improvement and integrated discriminatory improvement in the group with NTproBNP levels between 2000 and 8000 ng/l was 54% and 23%, respectively, and in the whole cohort 22% and 11%, respectively.

Conclusions: Our results suggested that, to assess risk in HF, older patients required significantly higher levels of NTproBNP than younger patients. Furthermore, a risk score that included TnT and CysC at discharge, and age could improve risk stratification for mortality in older patients with HF in particular when NTproBNP was moderately elevated.

ARTICLE SUMMARY

Article focus

- Our aim was to develop a multimarker prognostic score for improved risk stratification in decompensated heart failure (HF) in the elderly.

Key messages

- A composite risk score including cystatin C (CysC) over 1.3 mg/l, troponin T (TnT) over 10 ng/l and age over 75 years could identify a high-risk and low-risk groups ($p<0.0001$) for 3-year mortality in elderly patients with decompensated HF.
- Optimal N-terminal brain natriuretic peptide (NTproBNP) levels for risk stratification in the elderly HF patients were <2000 , 2000–8000 and >8000 ng/l.
- The risk score could improve risk stratification for mortality in older patients with HF in particular when NTproBNP was moderately elevated, probably because of moderate NTproBNP elevations caused by other comorbidities.

Strengths and limitations of the study

- We were able to measure levels of *multiple biomarkers* in a hospital cohort of elderly patients with decompensated HF and assess their association with mortality.
- One potential weakness was that we were unable to include many of the novel biomarkers that are emerging in clinical practice, such as MR-proANP and Copeptin.

INTRODUCTION

Heart failure (HF) remains as one of the leading causes of death worldwide.^{1–4} With advancing age, the risk increases for HF mortality and associated comorbidity.^{5–8} Previous landmark clinical trials were mostly conducted in younger HF patients who were, on average, under 63 years old.^{9–11} In practice, however, the majority of patients with new-onset HF are older adults.¹² The lack of

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representative samples of older patients in previous clinical trials on HF has given rise to serious concerns about whether the results from studies on younger patients are relevant for an older population.^{11 13}

The risk of death for patients with HF could only be partly explained by established mortality risk factors, including the New York Heart Association (NYHA) functional class,¹⁴ the N-terminal brain natriuretic peptide (NTproBNP),¹⁵ and the left ventricular ejection fraction (LVEF).^{14 15} This is particularly true for older individuals, where HF often coexists with other life-threatening diseases. In this context, we hypothesised that NTproBNP alone is not sufficient enough as a prognostic indicator in elderly HF patients and additional biomarkers might have added value in more accurately predicting the prognosis of HF in older populations.

We have, therefore, evaluated the prognostic potential of NTproBNP with and without other biomarkers in a cohort of older individuals with HF that were admitted because of decompensated HF.

METHODS

Study cohort and diagnosis

During 2006 and 2007, we consecutively enrolled 131 HF patients aged ≥ 65 years. The patients were hospitalised because of decompensated HF at the HF Unit, Department of Medicine, Sahlgrenska University Hospital/Sahlgrenska, Gothenburg, Sweden. The diagnosis of HF was based on the European Society of Cardiology definition.¹⁶ Inclusion criteria were a documented diagnosis of HF and admitted to hospital because of symptoms, signs or clinical investigations indicating decompensated HF. The only exclusion criteria were not giving informed consent and age < 65 years.

A patient was defined as having chronic obstructive pulmonary disease (COPD) when an International Classification of Diseases (ICD) code containing J44 was present in the medical record any time prior to discharge, or as having renal failure when any of the ICD codes N18.2–N18.5 were present in the medical record prior to the index admission. The study protocol was approved by the Ethical Committee at the University of Gothenburg. Written informed consent was obtained from all patients, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Follow-up and outcomes

All patients were followed up according to clinical routine. The main outcome was all-cause mortality because older HF patients often die of non-cardiac causes related to comorbidity. Owing to the limited sample size we did not analyse disease-specific mortality. All patients were followed up for 36 months or until death (mean 2.1 ± 1.2 years). Demographic and clinical information were obtained from medical records, including age, gender, NYHA functional class, LVEF,

history of hypertension, ischaemic heart disease and atrial fibrillation.

Echocardiography

Echocardiography was performed at least once for each patient at the department of clinical physiology in our hospital using the available standard equipment. Echocardiologists were blinded to the biochemical data and the study protocol. LVEF was assessed using Simpson's Biplane Method and/or by visual assessment. Patients were kept lying in left decubitus position during the examination. No data on interoperator coefficient of variation were available.

Laboratory analysis

Blood samples were drawn with the patients lying on bed, in the morning on the day of discharge and put in a -70°C freezer without delay after proper preparation of serum. All serum samples were thawed and analysed in one single run at the Department of Clinical Chemistry at Sahlgrenska University Hospital. Serum NTproBNP was analysed with the Roche Elecsys system with a coefficient of variation (CV) between 3.7% and 5.0%. Serum cystatin C (CysC) was analysed with reagents from Dako and on Modular P 2551 with a CV between 2.3% and 4.1%. The values of CysC were used to calculate the estimated glomerular filtration rate (eGFR) based on a locally generated equation, $\text{GFR (ml/min/1.73 m}^2) = (85.47/\text{CysC (ng/l)}) - 9.64$. Troponin T (TnT) was analysed using fourth-generation assays on a Modular e701 with a limit of detection of 10 ng/l and a limit of quantification where the CV was below 10% of 35 ng/l.

All the other laboratory parameters examined were part of the routine laboratory services provided by the Clinical Chemistry Laboratory, Sahlgrenska University Hospital.

Statistical analysis

Cox regression models were used to evaluate possible associations between mortality and serum levels of biomarkers (NTproBNP, TnT, creatine and CysC) and clinical variables including age, sex, echocardiographic parameters and underlying diseases. Univariate comparisons between groups were calculated with median tests. Dichotomous variables were analysed with the χ^2 test. Receiver operating characteristic (ROC) curves were used to assess the prognostic properties of the prognostic score and of different levels of NTproBNP. Areas under the ROC curves (AUCs) were compared with the DeLong methodology. The log rank test was used to compare different strata in Kaplan-Meier analyses of survival. HR with CIs were collected from the outputs from Cox regression analyses. Net reclassification improvement (NRI) and integrated discriminatory improvement (IDI) were calculated using STATA NRI command and STATA IDI command syntax, respectively. In the NRI calculations two risk levels were selected; $> 50\%$ and $< 50\%$ mortality.

Statistical analyses were performed with SPSS V.19 and Medcalc V.12.1.3.0 or Stata V.12. All probabilities were two-tailed, and $p < 0.05$ were regarded as significant. No missing data existed for the variables included in the prognostic score, but for other tested variables, cases sometimes were excluded if data were missing, although no more than two cases in each analysis had to be excluded because of a high-degree of data availability.

RESULTS

Demographic and clinical characteristics

In total, 131 older patients with HF were included (table 1). The median age (IQR) was 74 (68–79) years, the mean

LVEF was $43.1 \pm 13.8\%$, and 53% were male (table 1). Among the variables, we found that age, NTproBNP, TnT, urea, creatine, CysC and history of renal failure differed significantly between those who died and those who survived over 3 years (table 1).

Factors associated with mortality

Kaplan-Meier plots were used to identify the best separation of three risk groups; low-risk, intermediate-risk, and high-risk groups based on visual appearance and followed by log-rank tests for verification of statistical significance. Total mortality was 53.4%. Patients with NTproBNP levels < 2000 ng/l ($n = 39$) had a significantly

Table 1 Comparisons between those who died and those who survived within 3 years of study initiation

n	All HF patients	Dead	Alive	p Value
	131 Median (IQR)	70 Median (IQR)	61 Median (IQR)	
Male (%)	53±0.50	51±0.50	56±0.50	0.57
Age (years)	74 (68–79)	77 (72–82)	70 (66–75)	$p < 0.001$
BMI (kg/m ²)	26 (23–30)	26 (22–29)	27 (23–30)	0.89
LVEF (%)	45 (30–55)	43 (29–55)	45 (31–55)	0.80
Lab variables				
ALP (µkat/l)	1.5 (1.1–1.9)	1.6 (1.2–2.0)	1.4 (1.1–1.8)	$p = 0.49$
ASAT (µkat/l)	0.5 (0.4–0.6)	0.5 (0.4–0.7)	0.5 (0.4–0.6)	$p = 0.97$
Bilirubin (µmol/l)	14 (7.6–20)	15 (7.4–18)	12 (7.7–20)	$p = 0.35$
UREA (mmol/l)	11 (7.5–14)	13 (8.8–17)	9 (6.6–12)	$p = 0.002$
Creatine (µmol/l)	105 (84–136)	115 (93–159)	94 (79–111)	$p < 0.007$
CRP (mg/l)	13 (2.5–32)	14 (2.5–32)	13 (2.5–28)	$p = 0.85$
Haptoglobin (g/l)	1.4 (0.9–2.0)	1.4 (0.5–2.0)	1.4 (0.9–2.0)	$p = 0.96$
IgG (g/l)	11 (9.4–14)	11 (8.3–14)	12 (9.6–13)	$p = 0.29$
IgM (g/l)	0.74 (0.53–1.1)	0.73 (0.52–1.2)	0.77 (0.55–1.0)	$p = 0.76$
LDL (mmol/l)	2.0 (1.1–2.9)	1.9 (1.4–2.6)	2.1 (1.6–2.5)	$p = 0.28$
Orosomucoid (g/l)	1.0 (0.84–1.4)	1.1 (0.9–1.4)	1.0 (0.8–1.2)	$p = 0.42$
TSH (mU/l)	2.0 (1.1–2.9)	2.0 (1.1–3.1)	1.8 (1.0–2.6)	$p = 0.61$
Cardiovascular biomarkers				
NTproBNP (ng/l)	4030 (1060–8300)	6095 (2555–10 600)	2270 (638–4855)	$p = 0.002$
TnT (ng/l)	0 (0–200)	100 (0–400)	0 (0–0)	$p < 0.001$
CK-MB (ng/ml)	3 (3–5)	4 (3–5)	3 (3–4)	$p = 0.050$
CysC (mg/l)	1.3 (1.1–1.6)	1.4 (1.3–1.8)	1.2 (1.1–1.4)	$p < 0.001$
Adiponectin (µg/ml)	18 (12–30)	20 (15–32)	13 (11–25)	$p = 0.43$
Cardiovascular diseases				
Ischaemic heart disease (%)	40±49	44±50	36±48	$p = 0.38$
Valve disease (%)	39±49	37±49	43±50	$p = 0.49$
Hypertension (%)	32±47	28±45	36±48	$p = 0.34$
Diabetes mellitus (%)	22±42	25±44	18±39	$p = 0.31$
Atrial fibrillation (%)	42±50	41±50	44±50	$p = 0.70$
Comorbidity (%)				
Stroke	14±35	14±35	15±36	$p = 0.91$
COPD	87±34	14±35	12±32	$p = 0.66$
Renal failure	6.8±25	11±32	1.6±13	$p = 0.022$
Medications (%)				
ACE inhibitors or ARB	62±0.49	51±50	75±43	$p = 0.003$
β-Blockers	67±0.47	63±49	71±46	$p = 0.39$
Diuretics	87±34	87±34	87±34	$p = 0.94$

ALP, alkaline phosphatase; ASAT, aspartate transaminase; CK-MB, creatine kinase–myocardial band isoenzyme; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; CysC, cystatin C; hypertension, systolic blood pressure > 140 and/or diastolic blood pressure > 90 ; diabetes, on diabetic medication; IgG, immunoglobulin G; IgM, immunoglobulin M; LDL, low-density lipoprotein; NTproBNP, N-terminal pro-B-type natriuretic peptide; stroke, ischaemic or haemorrhagic stroke in the past; TnT, troponin T; TSH, thyroid stimulating hormone.

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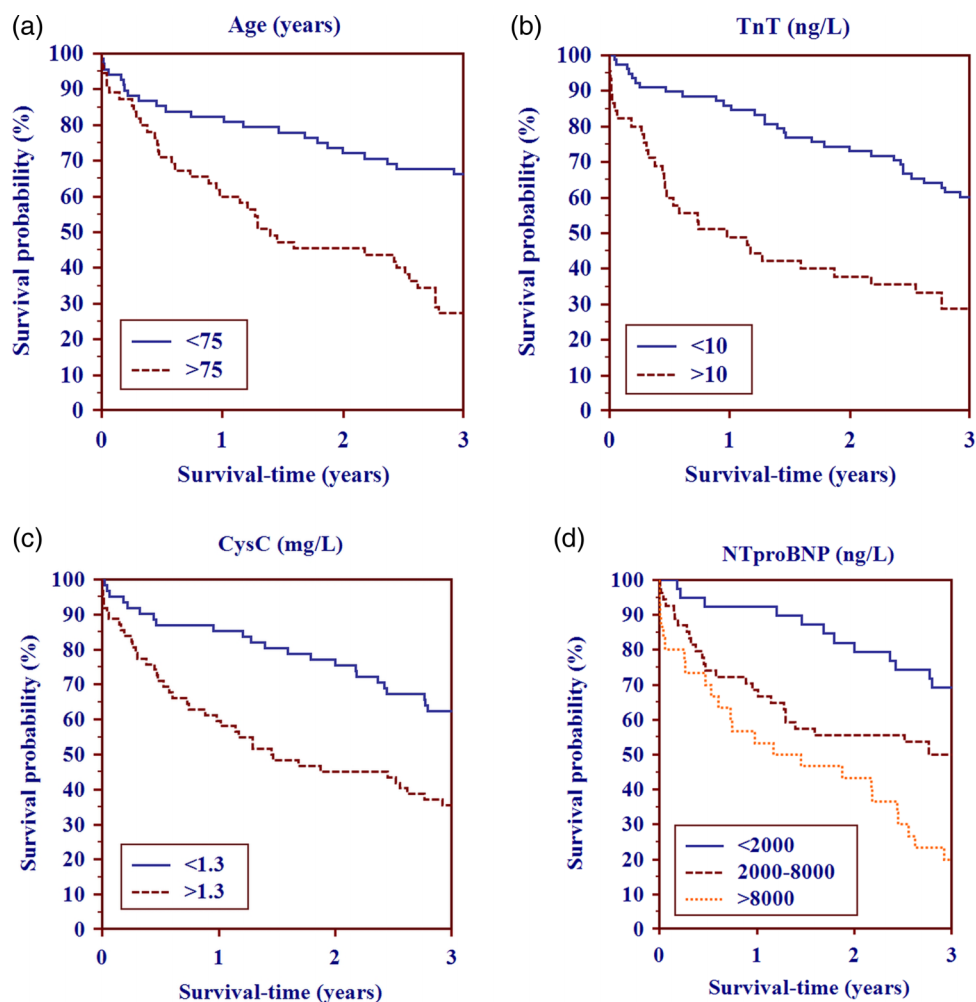


Figure 1 Kaplan-Meier plots show the relationship between 3-year mortality and significant variables (age, troponin T, TnT, and cystatin C, CysC) identified in multivariate analysis (and N-terminal brain natriuretic peptide, NTproBNP) (A–D). p Values for comparisons between strata are shown in table 3.

better prognosis (30.8% mortality) compared with patients with NTproBNP levels in the 2000–8000 range (n=58; 51.7% mortality) and patients with NTproBNP levels >8000 ng/l (n=34; 82.4% mortality; figure 1).

In univariate regression analyses, age, levels of creatinine, NTproBNP, TnT, creatine kinase MB, alkaline phosphatase, urea, CysC and orosomuroid were linked to mortality (tables 2 and 3). However, in multivariate

Table 2 Predictors of death within 3 years of study initiation, assessed with both univariate and multivariate analyses

Variables	Univariate		X ²	p Value	Multivariate		
	HR	95% CI			HR	95% CI	p Value
Age (years)	1.06	1.03 to 1.09	16.0	p<0.001	1.06	1.02 to 1.09	0.002
ALP (μkat/l)	1.09	1.02 to 1.16	8.05	p=0.010	1.08	0.98 to 1.18	0.13
UREA (mmol/l)	1.06	1.03 to 1.10	14.2	p<0.001	0.98	0.89 to 1.07	0.63
Creatinine (mol/l)	1.003	1.001 to 1.005	6.87	p=0.011	1.00	0.99 to 1.005	0.55
Orosomuroid (g/l)	2.15	1.12 to 4.15	5.26	p=0.022	1.24	0.57 to 2.68	0.59
NTproBNP (ng/l)	1.00006	1.00004 to 1.00009	28.5	p<0.001	1.000017	0.99997 to 1.00006	0.47
TnT (μg/l)	2.94	1.06 to 8.15	4.84	p=0.038	147.0	11.2 to 1929.8	<0.001
CK-MB (ng/ml)	1.11	1.002 to 1.23	4.05	p=0.045	0.93	0.76 to 1.13	0.45
CysC (mg/l)	2.56	1.70 to 3.85	20.4	p<0.001	6.57	1.80 to 24.0	0.004

ALP, alkaline phosphatase; ASAT, aspartate transaminase; CK-MB, creatine kinase–myocardial band isoenzyme; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; CysC, cystatin C; hypertension, systolic blood pressure>140 and/or diastolic blood pressure>90; diabetes, on diabetic medication; IgG, immunoglobulin G; IgM, immunoglobulin M; LDL, low-density lipoprotein; NTproBNP, N-terminal pro-B-type natriuretic peptide; stroke, ischaemic or haemorrhagic stroke in the past; TnT, troponin T; TSH, thyroid stimulating hormone. X²=51.0 for the multivariate model.

Table 3 p Values for comparisons between strata in Kaplan-Meier plots (figure 1) for 3-year mortality in elderly heart failure patients

Variable	p Value
Age	0.002
TnT	<0.0001
CysC	0.005
NTproBNP	<0.001

CysC, cystatin C; NTproBNP, N-terminal pro-B-type natriuretic peptide; TnT, troponin T.

analyses, only age, TnT and CysC remained prognostic (table 2).

Composite risk score

We generated a composite risk score based on the median values of three independent risk factors, age over 75 years (n=61), TnT over 10 ng/l (n=52) and CysC over 1.3 mg/l (n=70). The score levels were distributed as follows: 17 patients had 0 points, 49 patients 1 point, 50 patients 2 points and 16 patients 3 points. Each factor represented one point, and the score ranged from 0 to 3 (figure 2). Patients with a score of 0–1 points had a significantly better survival rate (79%) compared with patients with a score of 2–3 points (31%; $p<0.0001$) but there was no significant difference between 2 or 3 points (figures 2 and 3). The AUC for predicting 3-year mortality was 0.75 (95% CI 0.67 to 0.82; $p<0.0001$). When NTproBNP alone was tested as a predictive factor, it generated an AUC in the same range for the entire HF group, AUC=0.72 (95% CI 0.64 to 0.80; $p=0.58$). However, the NTproBNP level did not provide any

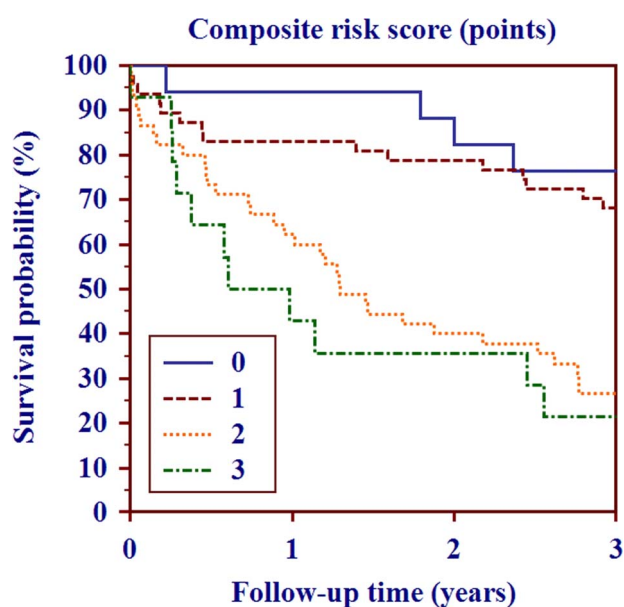


Figure 2 Kaplan-Meier plot shows the relationship between 3-year mortality and the composite risk factor score ($p<0.0001$ for linear trend).

Mortality within three years

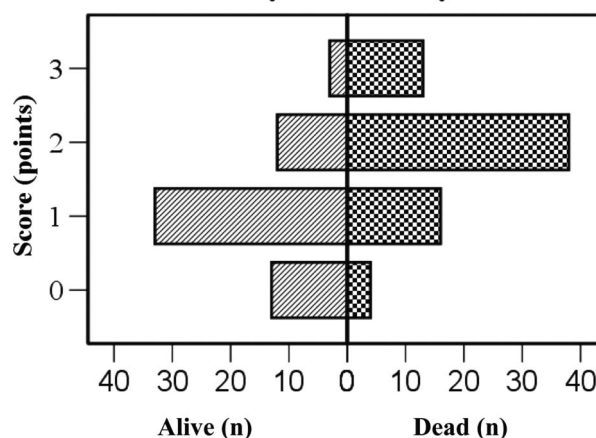


Figure 3 Distribution of the prognostic score among patients who died (right of 0) and survived (left of 0) within 3 years of inclusion in the study.

graded prognostic information within the range of 2000–8000 ng/l (AUC=0.53 (95% CI 0.40 to 0.67)). In this HF subgroup the composite risk score improved prognostic assessments (AUC=0.75; 95% CI 0.62 to 0.86; $p=0.03$). Among patients with a NTproBNP level between 2000 and 8000 ng/l 5 patients had 0 points, 22 patients 1 point, 25 patients 2 points and 6 patients 3 points, thus 27 patients were identified as low-risk (7/27 mortality; 26%) and 31 patients as high-risk individuals (23/31 mortality; 74%), $p<0.001$. When NTproBNP was above 8000 ng/l, 82.4% of patients died within 3 years, and the score did not add any prognostic information. Among patients with NTproBNP<2000, only 3% of patients had a composite risk score of 2–3; thus, the usefulness of the score could not be assessed in this subgroup.

Net reclassification improvement

Net reclassification improvement after adding the risk score to NTproBNP for improved risk classification (mortality risk above 50% or below 50%) was 54% in the NTproBNP range 2000–8000 ng/l and 22% in the whole cohort.

Integrated discrimination improvement

Integrated discrimination improvement after adding the risk score to NTproBNP for improved risk classification was 23% in the NTproBNP range 2000–8000 ng/l and 11% in the whole cohort.

DISCUSSION

This study included a real-life cohort of older patients with HF and comorbidity. They had been admitted because of decompensated HF. We found that a multimarker strategy could improve risk stratification for mortality within 3 years, in particular in patients with moderately elevated NTproBNP (2000–8000 ng/l). We

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also show that two cut-off values for NTproBNP are useful for identifying high-risk and low-risk individuals. An improved risk assessment would be of great clinical value for more accurately identifying older patients with HF that carries an increased risk of death. These patients should be targeted for more intensive treatment and closer monitoring. As health resources are restricted in the vast majority of the Western countries the need to give priority to high-risk individuals is well-known. Many factors were previously shown to predict adverse outcome in HF, including high age, history of diabetes mellitus or renal dysfunction, high NYHA class, low LVEF, low weight, low systolic blood pressure, the presence of ankle oedema and low quality-of-life scores.¹⁷ However, a few of those factors are strong prognostic predictors when evaluated separately. Moreover, assessments of those factors are typically difficult in clinical practice, particularly in older patients with comorbidity.

NTproBNP and BNP are important prognostic biomarkers in younger patients with HF. They appear to be better predictors of survival than many traditional prognostic indicators, including the NYHA class, serum creatinine and possibly LVEF.¹⁴ The relative risk of death among younger patients with HF was shown to increase by about 35% for each 100 pg/ml increase in BNP.^{14 18} Therefore, BNP or NTproBNP assessments have been emphasised in the European Society of Cardiology guidelines.¹⁶ However, most prognostic studies that included BNP or NTproBNP assessments were performed in patients whose mean age was under 68 years;¹⁴ thus, the predictive power of BNP and NTproBNP lack sufficient validation in older patients with HF. The present study indicated that substantially higher levels of NTproBNP should be used for risk stratifications of older patients with HF. For example, NTproBNP levels of <300 ng/l, 300–1500 ng/l, and >1500 ng/l are recommended for stratification of risk based on studies in younger cohorts.¹⁶ In contrast, in older decompensated HF patients we found that NTproBNP levels of <2000, 2000–8000 and >8000 ng/l could optimally separate the HF-cohort into low-risk, moderate-risk and high-risk groups. In agreement with previous studies,¹⁹ we found that NTproBNP was a significant predictor in univariate, but not in multivariate analyses. This can be explained by the fact that NTproBNP levels are linked to several other factors that affect prognosis in HF, including low LVEF, pulmonary disease and renal disease which are common among older patients.

In addition, a single biomarker is not always sufficient for risk assessment in an older population with HF, where comorbidity is common. Consequently, there is a need for applying a multimarker strategy that can provide adequate risk assessment. Horwich *et al* studied 238 patients (mean age 53 years) with advanced HF who had been referred for cardiac transplantation evaluation. They found that the level of cardiac troponin I combined with the level of BNP improved the prediction of all cause deaths or an urgent need for cardiac

transplantation.²⁰ Ishino *et al* studied 164 patients with HF (mean age 68 years old). They reported that the combined levels of BNP, heart-type fatty acid-binding protein and pentraxin three could improve the prediction of cardiac death or hospitalisation because of worsening of HF.¹⁹ However, there are only a limited number of studies using a multimarker strategy for prognostic assessment in older patients with HF.

In this study, we developed a composite risk score based on age, TnT and CysC levels, biomarkers known to have prognostic value for patients with HF.^{20 21} This composite risk score was able to differentiate older patients with HF into high-risk and low-risk groups. The score was particularly useful among older patients with HF who had moderately elevated NTproBNP, a group that is often difficult to evaluate. We suggest that this composite risk score should be used as a prognostic algorithm for older patients with HF that have NTproBNP levels in the range 2000–8000 ng/l. However, it is possible to use the score at all NTproBNP levels.

However, the score must be validated in an independent and larger cohort before it can safely be implemented in clinical routine. The sample size is also rather small so the results should be interpreted with caution.

It is already established that renal function, TnT as well as age can provide independent prognostic information, but our study focuses on how these markers can be dichotomised and combined into a simple prognostic scoring algorithm that is memorisable and easily applied by busy clinicians. Successful therapeutic intervention could possibly lead to decreasing levels of TnT and CysC. This could generate fewer points in the prognostic score and thus imply a better prognosis, something that has to be evaluated in a future study.

In this exploratory study we chose to include a sample size of 131 patients to be able to test multiple biomarkers at a reasonable cost and generate useful hypotheses for future research. We chose to study all-cause mortality because it is robust and not prone to reporting bias. We also believe that all-cause mortality is more important in the elderly since they can die because of non-cardiac reasons.

In conclusion, by assessing multiple biomarkers at discharge, our data suggest that, when NTproBNP levels are between 2000 and 8000 ng/l, a composite risk factor score that includes the levels of TnT, CysC and age provided superior risk stratification for mortality compared with NTproBNP alone.

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Contributors The five authors are justifiably credited with authorship, according to the authorship criteria. CB was involved in conception, design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, final approval; JJ in design, acquisition of data, final approval given; MP in analysis and interpretation of data; OH in interpretation of data, drafting of the manuscript, final approval; and MF in conception, design, interpretation of data, drafting of the manuscript and final approval.

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Competing interests None.

Ethics approval The study protocol was approved by the Ethical Committee at the University of Gothenburg. Written informed consent was obtained from all patients, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement There are no additional data available.

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