Cardiac Biomarkers Retain Prognostic Significance in Patients with Heart Failure and COPD

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a frequent comorbidity in patients with heart failure (HF). We assessed the influence of COPD on circulating levels and prognostic value of 3 HF biomarkers: N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hs-TnT), and soluble suppression of tumorigenesis-2 (sST2).

Methods: Individual data from patients with chronic HF, known COPD status, NT-proBNP and hs-TnT values (n=8,088) were analysed. A subgroup (n=3,414) had also sST2 values.

Results: Patients had a median age of 66 years (interquartile interval 57-74), 77% were men, and 82% had HF with reduced ejection fraction. NT-proBNP, hs-TnT and sST2 were 1,207 ng/L (487-2,725), 17 ng/L (9-31), and 30 ng/mL (22-44), respectively. Patients with COPD (n=1,249, 15%) had higher NT-proBNP (p=0.042) and hs-TnT (p<0.001), but not sST2 (p=0.165). Over a median 2.0-year follow-up (1.5-2.5), 1,717 patients (21%) died, and 1,298 (16%) died from cardiovascular causes; 2,255 patients (28%) were hospitalized for HF over 1.8 years (0.9-2.1). NT-proBNP, hs-TnT and sST2 predicted the 3 endpoints regardless of COPD status. The best cut-offs from receiver operating characteristics analysis were higher in patients with COPD than those without. Patients with all 3 biomarkers higher than or equal to endpoint- and COPD status-specific cut-offs were also those with the worst prognosis.

Conclusions: Among patients with HF, those with COPD have higher NT-proBNP and hs-TnT, but not sST2. All these biomarkers yield prognostic significance regardless of the COPD status.

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Introduction

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are disabling chronic conditions. Up to 20% of patients with HF have also COPD [1,2], although the prevalence of comorbid COPD is likely underestimated and often undiagnosed [3,4]; conversely, many patients with a diagnosis of COPD may also have "masked", unsuspected HF [5]. HF and COPD share common risk factors, including older age, smoking and obesity, and may have similar presentation, usually characterized by dyspnoea and reduced exercise tolerance. Furthermore, patients with severe COPD display weight loss, muscle wasting and severe functional limitations overlapping with clinical features of advanced HF [6]. COPD has been associated with worse outcome in patients with HF, both in study registries such as the HF Long-Term Registry of the European Society of Cardiology [7] and in *post-hoc* analyses of clinical trials such as the SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) trial [1]. The interplay between COPD diagnosis, HF biomarkers and outcome has been less extensively explored.

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) do not display a prominent increase in patients with stable COPD but no HF, but can be elevated and hold prognostic value in patients with COPD exacerbations [8,9]. Conversely, patients with stable chronic HF and also COPD have higher NPs than those with HF but no COPD [5]. In patients hospitalized for acute HF and evaluated after haemodynamic stabilization, COPD severity, measured as the forced expiratory volume in the first second or alveolar volume, was correlated with NT-proBNP [10,11].

Troponin T (TnT) and soluble suppression of tumorigenesis-2 (sST2) are other HF biomarkers with an established prognostic value. Circulating TnT is higher in patients with HF and COPD than in those without COPD [12,13]. In a small study, the median sST2 concentration was 2.5-fold higher in patients with HF, and 5-fold higher in patients with COPD than controls (n=15 in all groups) [14-16]. In a larger cohort, Martinez-Rumayor et al. reported that higher sST2 yielded prognostic significance among patients with primary pulmonary disorders, including COPD, although sST2 was measured through an early generation, lower-precision assay [17].

In the present paper we focused on the relationship between COPD status, circulating levels and prognostic value of NT-proBNP, hs-TnT, and sST2 in a large international cohort of patients with chronic HF.

Methods

Patient population

The BIomarkers Of heart failure Study (BIOS) consortium includes 14 cohorts of patients with stable chronic HF. This consortium was created by merging the dataset created for a previous individual patient data meta-analysis on hs-TnT and outcome (n=9,289) [18] with other cohorts of patients with stable HF, namely the Prospective Evaluation of Outcome in Patients with heart failure with preserved Left ventricular Ejection fraction (PEOPLE), the Singapore Heart failure Outcomes and Phenotypes (SHOP) cohorts (n=941 and 1,099, respectively) [19], an additional cohort of HF outpatients from the Hospital Universitari Germans Trial i Pujol, Barcelona, Spain (n=1,589), and an Institutional dataset of the Fondazione Toscana Gabriele Monasterio, Pisa, Italy (n=2,763). The total patient number was 15,681. For the present study we considered only the patients (n=8,088) with available NT-proBNP and hs-TnT and COPD status (present or absent) adjudicated based on the clinical judgment of the investigators of the original cohorts, taking into account the patient's medical history, treatment and/or spirometry data.

Laboratory evaluation

In all studies, NT-proBNP was measured through the monoclonal electrochemiluminescence immunoassay method (Roche Diagnostics®; coefficient of variation [CV] <3% at cut-off value [150 ng/L]) [20], and TnT through the Roche Diagnostics® assay (Basel, Switzerland; limit of blank 3 ng/L, limit of detection [LOD] 5 ng/L, 99th percentile value in apparently healthy individuals of 14 ng/L) [21]. In a subgroup of patients (n=3,418, 26%), sST2 was measured through the Presage® assay (LOD 1.3 ng/mL, measurement range up to 200 ng/mL, intra-assay CV <7%, inter-assay CV <9%)

[22]. These biomarkers were assayed in a core laboratory for each study. Samples were collected during an outpatient visit; patients had been clinically stable, with no need for changes in therapy for at least 1 month. The estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology collaboration equation [23]; patients on dialysis were excluded.

Statistical analysis

IBM SPSS Statistics (version 22, 2013) and R statistical software (http://www.r-project.org/, version 3.4.4) were used. Normal distribution was assessed by plotting a histogram and running the Kolmogorov-Smirnov test; variables with normal distribution were presented as mean ± standard deviation, while those with non-normal distribution as medians and interquartile intervals. Missing data were discarded and not imputed. Mean differences among groups were evaluated through the unpaired Student T-test or the Mann–Whitney U test, as appropriate. Categorical variables were compared by the Chi-square test with Yates correction. The β coefficients were computed at multivariate linear regression analysis. Multicollinearity was searched by calculating the Variance Inflation Factor, with a threshold of 5. Schoenfeld residuals were evaluated to check the proportional hazards assumption. Uni- and multivariate Cox regression analysis was performed to search for predictors of 3 endpoints: all-cause death, cardiovascular death, and HF hospitalization. The Fine-Gray model was used to account for mutually exclusive endpoints; non-cardiovascular death was considered as a competing risk for cardiovascular death, and all-cause death for HF hospitalization. The multivariate models for the 3 endpoints included all univariate predictors with $p < 0.050$, excluding colinear variables. Separate models were created for patients with NT-proBNP and hs-TnT values or those with also sST2 values: 1) all-cause death, NT-proBNP and hs-TnT: age, sex, New York Heart Association (NYHA) class III-IV, eGFR, left ventricular ejection fraction (LVEF), therapy with beta-blockers, COPD, NT-proBNP and hs-TnT; 2) all-cause death, NT-proBNP, hs-TnT and sST2: age, sex, NYHA III-IV, LVEF, beta-blockers, NT-proBNP, hs-TnT, sST2; 3) cardiovascular death, NT-proBNP and hs-TnT: age, sex, NYHA III-IV, eGFR, LVEF, beta-blockers,

NT-proBNP, hs-TnT; 4) cardiovascular death, NT-proBNP, hs-TnT and sST2: age, sex, NYHA III-IV, eGFR, LVEF, beta-blockers, NT-proBNP, hs-TnT, sST2; 5) HF hospitalization, NT-proBNP and hs-TnT: diabetes, NYHA III-IV, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), mineralocorticoid receptor antagonists (MRA), COPD, NT-proBNP, hs-TnT; 6) HF hospitalization, NT-proBNP, hs-TnT and sST2: body mass index, diabetes, NYHA III-IV, eGFR, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), mineralocorticoid receptor antagonists (MRA), COPD, NT-proBNP, hs-TnT, sST2 (**Table 3**). Cubic spline interpolation was carried out to represent the changes in risk according to biomarker values; 5 knots were considered. Area under the curve values were compared through the DeLong's test, and the best cut-offs were searched through the Youden method. Two-tailed p values <0.05 were deemed significant.

Results

Patient population

Patients (n=8,088) had a median age of 66 years (interquartile interval 57-74), 77% were men, and 82%, 6%, 8% had HF with reduced, mid-range, or preserved ejection fraction (HFrEF/HFmrEF/HFpEF), respectively (the remaining patients had missing LVEF data). Patients with COPD (n=1,249, 15%) were older (age 70 years [62-77] vs. 65 [56-73]; p<0.001) and more often men (80% vs. 77%; p=0.019), had more severe dyspnoea (46% in New York Heart Association class III-IV vs. 33%; p<0.001), and were less often on beta-blockers (46% vs. 59%, p<0.001; **Table 1**).

COPD and biomarkers

In the whole cohort, NT-proBNP and hs-TnT were 1,207 ng/L (487-2,725) and 17 ng/L (9-31), respectively. In the subgroup with sST2 values available (n=3,414), sST2 was 30 ng/mL (22-44).

Patients with COPD had higher NT-proBNP (p=0.042) and hs-TnT (p<0.001). sST2 did not differ significantly between patients with COPD (n=491, 14%) vs. those without (p=0.165; **Table 1**).

Predictors of NT-proBNP, hs-TnT and (in the subgroup with available values) sST2 were searched among population characteristics from **Table 1**. COPD independently predicted hs-TnT, while it was just a univariate predictor of NT-proBNP, and did not predict sST2 even at univariate analysis (**Table 2**). Similar results emerged from an analysis restricted to patients with HFrEF (**Supplemental Table 1**).

COPD, biomarkers and outcome

Over a median 2.0-year follow-up (1.5-2.5), 1,717 patients (21%) died, and 1,298 (16%) died from cardiovascular causes. Furthermore, 2,255 patients (28%) were hospitalized for HF over 1.8 years (0.9-2.1). For each one of the 3 endpoints we searched the univariate predictors among baseline characteristics, and we included them in multivariate models. COPD predicted all-cause death and HF hospitalization independently from NT-proBNP and hs-TnT, but lost its independent prognostic value when sST2 was included in the model (decreasing the number of patients available for analysis). Conversely, NT-proBNP, hs-TnT and sST2 predicted the 3 endpoints regardless of COPD status (**Table 3**). In patients with HFrEF, COPD status did not independently predict all-cause or cardiovascular death, while it predicted HF hospitalization independently of NT-proBNP and hs-TnT, but not sST2 (**Supplemental Table 2**).

Influence of COPD on the prognostic value of biomarkers

NT-proBNP, hs-TnT and sST2 were all univariate predictors of outcome, and the risk of all-cause death, cardiovascular death and HF hospitalization increased exponentially with rising biomarkers, in both patients with COPD and those without (**Figure 1**). In both subgroups, NT-proBNP and hs-TnT displayed similar AUC values, and higher than sST2 (**Figure 2** and **Supplemental Table 4**). The best cut-offs were always higher in patients with COPD than those without (**Table 4** and

Supplemental Table 5). In both subgroups with or without COPD, patients with all 3 biomarkers higher than or equal to endpoint- and COPD status-specific cut-offs were also those with the worst prognosis (**Figure 3**). The best cut-offs in patients with HFrEF were quite close than those calculated in the whole population (**Supplemental Table 6**).

Discussion

In a large cohort of patients with chronic HF (n=8,088), patients with COPD (n=1,249, 15%) had higher levels of NT-proBNP and hs-TnT (both $p<0.001$), but not sST2 ($p=0.165$). NT-proBNP, hs-TnT and sST2 predicted the 3 endpoints regardless of COPD status. The best cut-offs from receiver operating characteristics analysis were higher in patients with COPD than those without. When stratifying patients based on endpoint- and COPD status-specific cut-offs, the frequency of the endpoints increased rapidly together with the number of biomarkers ≥cut-offs.

The comparison between patients with or without COPD confirms the association between this condition and a clinical profile characterized by more advanced age, more severe symptoms and comorbidities. Several factors, such as age [24], lower eGFR values [25], AF [26], and lower body mass index [27], have been previously associated with higher NT-proBNP; accordingly, circulating NT-proBNP was significantly higher in patients with COPD, but COPD did not display an independent relationship with NT-proBNP. As for hs-TnT, its levels are higher in men and in elderly subjects, leading to the proposal of age-adjusted cut-offs to diagnose myocardial infarction [28]. The age-dependent increase of hs-TnT seems partially explained by the concurrent growing burden of comorbidities [29], and reduced renal clearance [30]. The relationship between COPD and hs-TnT was even tighter than the one with NT-proBNP or sST2, again possibly because of age, renal dysfunction and comorbidities, but likely also as a result of detrimental effects of chronic inflammation on the myocardium [31]. sST2 is classified among inflammatory biomarkers, reflecting the body of evidence indicating a role in inflammatory disorders also beyond the cardiovascular system [32]. The lungs are among the main sites of sST2 production, even in patients with HF [33,34],

and sST2 may blunt IL-33-mediated inflammation in COPD [15]. The finding that sST2 is less affected by the COPD status than NT-proBNP and hs-TnT was therefore unexpected. Nonetheless, a wide distribution of sST2 values with a large overlap between patients with HF and HF plus pneumonia or COPD was previously reported [16,35]. One explanation might be that sST2 concentrations are less affected than those of NT-proBNP and hs-TnT by age and renal dysfunction [36,37]. We should also remember that sST2 was evaluated in a much smaller number of patients than NT-proBNP and hs-TnT.

All 3 biomarkers displayed a similar, exponential relationship with all-cause and cardiovascular death and HF hospitalization; hs-TnT and sST2 cut-offs refined risk prediction over the NT-proBNP cut-off alone, confirming the additive prognostic value of hs-TnT and sST2 to NT-proBNP previously reported in the broader population of patients with HF [38]. Therefore, a panel including NT-proBNP, hs-TnT and sST2 assays may help predict the risk of hard endpoints such as all-cause and cardiovascular mortality, as well as HF hospitalization, but higher cut-offs should be preferably considered in patients with COPD. Whether the more accurate risk stratification derived from our findings can be translated into better patient management ultimately leading to improved patient prognosis, remains an open question which should be addressed in dedicated studies.

Limitations

An important study limitation is that the database was created to assess the relationship between circulating biomarkers and outcome, rather than the clinical and prognostic correlates of conditions such as COPD. This comorbidity was recorded in the case report forms according to prespecified criteria for data collection, and it was not possible to ascertain how many patients had undergone pulmonary function testing. Similarly, data on disease severity, smoking habit, or specific therapies were not available. On the other hand, the lack of further details on the COPD diagnosis is a limitation shared with sub-analyses of other registry studies such as the large HF Long-Term Registry [7]. Relevant data such as the size and function of right heart chambers were not collected. Even HF

aetiology was not available in most studies, which did not allow us to correlate biomarker levels with specific conditions. Data collection spanned across 3 decades, from 1997 (when enrolment in the Val-HeFT trial began) to 2020, during a period of great advances in HF treatment. Furthermore, patients with HFmrEF or HFpEF accounted for just 14% of the whole cohort; this does not reflect the real-world HF epidemiology, and does not allow to extent study conclusions to patients with HFmrEF and HFpEF while increasing population heterogeneity. Additionally, sST2 was measured in 36% of patients, as opposed NT-proBNP and hs-TnT measurement in the whole cohort. Despite extensive adjustment in multivariable models, an effect of residual confounders cannot be excluded. Finally, we did not assess the risk of non-cardiovascular mortality and hospitalization, although these endpoints are clinically relevant in patients with COPD and were specifically analysed in the Val-HeFT cohort [11].

Conclusions

Among patients with HF, those with COPD have higher NT-proBNP and hs-TnT, but not sST2. All these biomarkers yield prognostic significance regardless of the COPD status.

Disclosures

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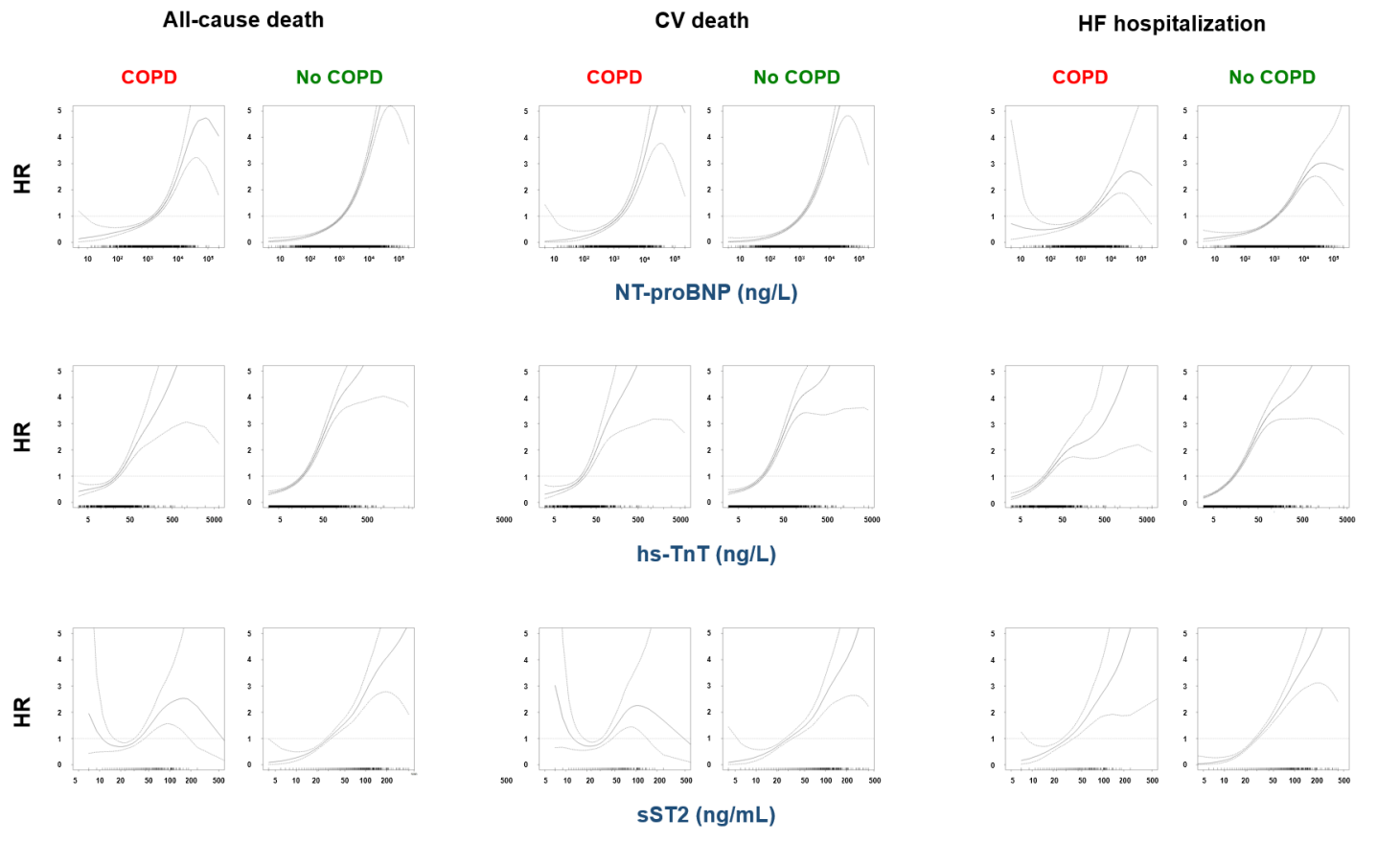
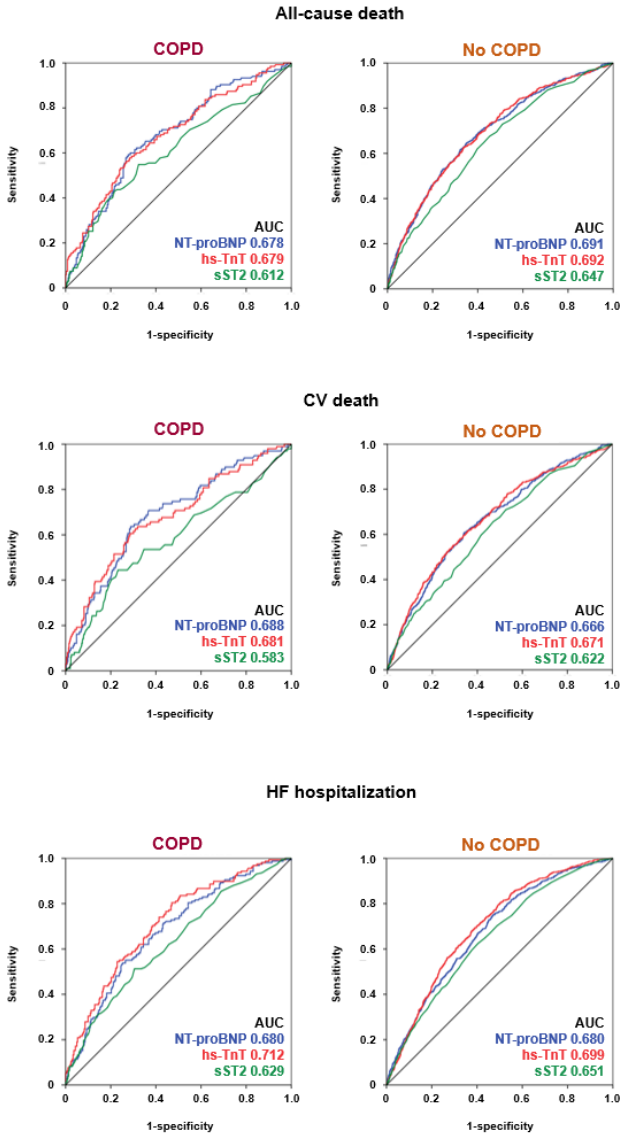
Figures

Figure 1. Circulating biomarkers and patient survival: spline curve analysis.



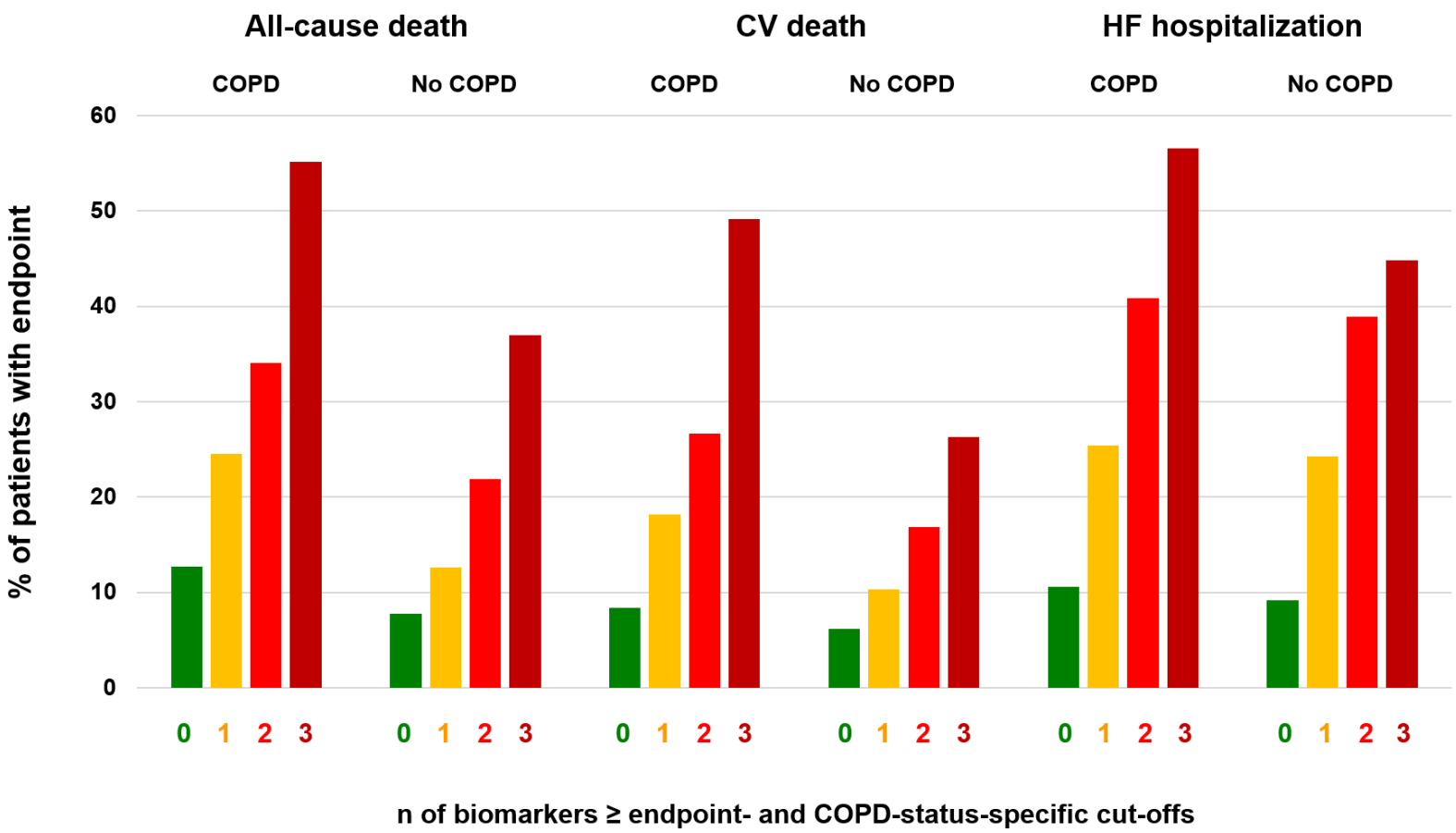
COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenesis-2.

Figure 2. Biomarkers for outcome prediction: area under the curve (AUC) values.



COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenesis-2. The p values for the comparisons between AUC values are reported in the **Supplemental Table 2**.

Figure 3. Number of elevated biomarkers and risk of outcome.



The best prognostic cut-offs were searched for each endpoint and for the chronic obstructive pulmonary disease (COPD) status (present or absent). These endpoint- and COPD status-specific biomarkers are reported in **Table 3**. Patients were categorized according to the number of biomarkers higher than or equal to these cut-offs. The percentages of patients experiencing the 3 endpoints are reported as a function of this number.

Table 1. Patient characteristics.

Variable	Missing values, n (%)	Whole population n=8,088	COPD		p
			Yes (n=1,249, 15%)	No (n=6,839, 85%)	
Age (years)	0 (0)	66 (57-74)	70 (62-77)	65 (56-73)	**<0.001**
Men, n (%)	0 (0)	6,249 (77)	997 (80)	5,252 (77)	**0.019**
BMI (kg/m^2)	210 (3)	26 (24-30)	27 (24-31)	26 (24-30)	**<0.001**
Hypertension, n (%)	6 (0)	4,300 (53)	734 (59)	3,566 (52)	**<0.001**
Diabetes, n (%)	2 (0)	2,574 (32)	409 (33)	2,165 (32)	0.451
AF, n (%)	5 (0)	1,799 (22)	360 (29)	1,439 (21)	**<0.001**
NYHA III-IV, n (%)	188 (2)	2,854 (35)	569 (46)	2,285 (33)	**<0.001**
eGFR (mL/min/1.73 m^2)	52 (1)	58 (46-70)	56 (44-79)	58 (46-70)	**0.012**
LVEF (%)	267 (3)	30 (23-36)	30 (24-38)	29 (23-36)	**<0.001**
LVEF <40%, 40-49%, ≥50%, n (%)	267 (3)	6,631, 517, 673 (82, 6, 8)	941, 110, 137 (75, 9, 11)	5,690, 407, 536 (83, 6, 8)	**<0.001**

Beta-blockers, n (%)	1 (0)	4,635 (57)	570 (46)	4,065 (59)	**<0.001**
ACEi/ARB, n (%)	6 (0)	7,010 (87)	1,074 (86)	5,936 (87)	0.442
MRA, n (%)	8 (0)	1,802 (22)	322 (26)	1,480 (22)	**0.001**
NT-proBNP (ng/L)	0 (0)	1,207 (487-2,725)	1,370 (580-2,942)	1,173 (472-2,677)	**0.042**
hs-TnT (ng/L)	0 (0)	17 (9-31)	22 (13-38)	17 (9-30)	**<0.001**
sST2 (ng/mL)	4,674 (58)	30 (22-44)	31 (23-45)	29 (21-43)	0.165

ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers; AF, atrial fibrillation; BMI; body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; hs-TnT, high-sensitivity troponin T; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenesis-2.

Table 2. Predictors of biomarker levels.

	NT-proBNP n=8,088				hs-TnT n=8,088				sST2 n=3,414			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	p	Beta	p	Beta	p	Beta	p	Beta	p	Beta	p	Beta
Age	<0.001	0.243	<0.001	0.114	<0.001	0.102	<0.001	0.057	<0.001	0.118	0.044	0.041
Men	<0.001	0.052	<0.001	0.041	0.488	-	-	-	0.050	-	-	-
BMI	<0.001	-0.206	<0.001	-0.179	0.001	-0.039	0.003	-0.035	<0.001	-0.097	<0.001	-0.068
Hypertension	<0.001	0.096	<0.001	0.058	<0.001	0.056	0.043	0.024	0.010	0.044	0.625	-
Diabetes	<0.001	0.074	<0.001	0.060	<0.001	0.083	<0.001	0.070	<0.001	0.072	<0.001	0.063
AF	<0.001	0.124	<0.001	0.105	0.003	0.033	0.289	-	<0.001	0.125	<0.001	0.089
NYHA III-IV	<0.001	0.174	<0.001	0.108	<0.001	0.072	<0.001	0.049	<0.001	0.104	<0.001	0.089
eGFR	<0.001	-0.255	<0.001	-0.174	<0.001	-0.099	<0.001	-0.061	<0.001	0.100	<0.001	-0.081
LVEF	<0.001	-0.078	<0.001	-0.133	0.642	-	-	-	0.049	0.034	0.727	-

LVEF <40%, 40-49%, ≥50%	0.708	-	-	-	0.102	-	-	-	<0.001	0.081	-	-
Beta-blockers	<0.001	0.056	<0.001	0.069	0.784	-	-	-	<0.001	0.106	<0.001	0.070
ACEi/ARB	<0.001	-0.085	<0.001	-0.052	0.208	-	-	-	<0.001	-0.098	<0.001	-0.074
MRA	<0.001	0.095	<0.001	0.067	<0.001	0.045	<0.001	0.042	<0.001	0.121	<0.001	0.096
COPD	0.042	0.023	0.818	-	<0.001	0.050	0.001	0.036	0.165	-	-	-

Values of N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hs-TnT) and soluble suppression of tumorigenesis-2 (sST2) were log_2-transformed. AF, atrial fibrillation; BMI; body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction.

Table 3. Predictors of outcome.

	All-cause death					CV death					HF hospitalization				
	Univa-riate	Multivariate NT-TnT (n=7,626)		Multivariate NT-TnT-sST2 (n=3,299)		Univa-riate	Multivariate NT-TnT (n=7,626)		Multivariate NT-TnT-sST2 (n=3,299)		Univa-riate	Multivariate NT-TnT (n=6,975)		Multivariate NT-TnT-sST2 (n=3,183)	
	p	p	HR (95% CI)	p	HR (95% CI)	p	p	HR (95% CI)	p	HR (95% CI)	p	p	HR (95% CI)	p	HR (95% CI)
Age	<0.001	<0.001	1.01 (1.01-1.02)	0.002	1.01 (1.01-1.02)	<0.001	0.002	1.01 (1.00-1.02)	0.012	1.01 (1.00-1.02)	<0.001	0.379	-	0.562	-
Men	0.003	<0.001	1.31 (1.16-1.49)	0.043	1.21 (1.07-1.45)	0.001	<0.001	1.38 (1.20-1.60)	0.015	1.30 (1.05-1.62)	0.712	-	-	-	-
BMI	<0.001	0.215	-	0.292	-	<0.001	0.849	-	0.978	-	0.037	0.063	-	0.018	1.02 (1.00-1.03)
Hypertension	<0.001	0.318	-	0.975	-	0.061	-	-	-	-	<0.001	0.099	-	0.729	-
Diabetes	<0.001	0.156	-	0.989	-	<0.001	0.327	-	0.984	-	<0.001	<0.001	1.19	<0.001	1.37

													(1.09-1.31)		(1.20-1.58)
AF	<0.001	0.931	-	0.795	-	<0.001	0.524	-	0.919	-	<0.001	0.683	-	0.195	-
NYHA III-IV	<0.001	<0.001	1.42 (1.28-1.57)	<0.001	1.41 (1.21-1.65)	<0.001	<0.001	1.46 (1.30-1.64)	<0.001	1.57 (1.31-1.89)	<0.001	<0.001	1.17 (1.07-1.28)	<0.001	1.31 (1.14-1.49)
eGFR	<0.001	<0.001	0.99 (0.99-0.99)	0.117	-	<0.001	<0.001	0.99 (0.99-1.00)	<0.001	0.99 (0.99-1.00)	<0.001	0.373	-	0.010	1.00 (0.99-1.00)
LVEF	<0.001	0.004	0.99 (0.99-1.00)	0.013	0.99 (0.98-1.00)	<0.001	<0.001	0.99 (0.98-0.99)	<0.001	0.99 (0.98-0.99)	0.002	0.490	-	0.238	-
LVEF <40%, 40-49%, 50%	0.128	-	-	-	-	0.001	-	-	-	-	<0.001	-	-	-	-
Beta-blockers	<0.001	<0.001	1.41 (1.27-1.56)	<0.001	1.43 (1.23-1.68)	<0.001	<0.001	1.45 (1.30-1.63)	<0.001	1.55 (1.30-1.86)	<0.001	0.055	-	0.102	-
ACEi/ARB	0.032	0.577	-	0.577	-	0.858	-	-	-	-	<0.001	<0.001	0.65 (0.58-0.72)	0.008	0.79 (0.66-0.94)
MRA	0.940	-	-	-	-	0.746	-	-	-	-	<0.001	<0.001	1.64 (1.49-1.81)	0.001	1.28 (1.10-1.48)

COPD	<0.001	0.019	1.16 (1.03-1.31)	0.710	-	<0.001	0.289	-	0.931	-	<0.001	0.001	1.28 (1.08-1.35)	0.154	-
NT-proBNP	<0.001	<0.001	1.25 (1.20-1.30)	<0.001	1.14 (1.07-1.21)	<0.001	<0.001	1.25 (1.20-1.31)	0.001	1.12 (1.05-1.20)	<0.001	<0.001	1.11 (1.08-1.51)	<0.001	1.14 (1.08-1.20)
hs-TnT	<0.001	<0.001	1.27 (1.21-1.32)	<0.001	1.26 (1.18-1.34)	<0.001	<0.001	1.26 (1.20-1.32)	<0.001	1.25 (1.17-1.34)	<0.001	<0.001	1.27 (1.23-1.32)	<0.001	1.24 (1.17-1.31)
sST2	<0.001			<0.001	1.27 (1.16-1.40)	<0.001			<0.001	1.24 (1.11-1.39)	<0.001			<0.001	1.29 (1.19-1.41)

Values of N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hs-TnT) and soluble suppression of tumorigenesis-2 (sST2) were log_2-transformed. Univariate predictors of the 3 endpoints were then included in multivariate models. When both left ventricular ejection fraction (LVEF) and LVEF categories emerged as univariate predictors, the latter was not included in the model. The number of patients available for analysis decreased substantially when including sST2 in the model. AF, atrial fibrillation; BMI; body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.

Table 4. Best cut-offs for outcome prediction in patients with or without chronic obstructive pulmonary disease (COPD).

	All-cause death n=1,717 (21%)		CV death n=1,298 (16%)		HF hospitalization n=2,255 (28%)	
	COPD (n=1,249, 15%)	**No COPD (n=6,839, 85%)**	**COPD (n=1,249, 15%)**	**No COPD (n=6,839, 85%)**	**COPD (n=1,249, 15%)**	**No COPD (n=6,839, 85%)**
NT-proBNP (ng/L)	2,263	1,639	2,263	1,646	1,288	1,007
hs-TnT (ng/L)	31	18	30	18	19	15
sST2 (ng/mL)	37	30	44	30	37	30

The sensitivity and specificity values for each cut-off are reported in **Supplemental Table 5**. CV, cardiovascular; HF, heart failure; hs-TnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenesis-2.