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Original Article

Acutely decompensated heart failure with chronic obstructive pulmonary disease: Clinical characteristics and long-term survival

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is among the most common comorbidities in patients hospitalized with heart failure and is generally associated with poor outcomes. However, the results of previous studies with regard to increased mortality and risk trajectories were not univocal. We sought to assess the prognostic impact of COPD in patients admitted for acutely decompensated heart failure (ADHF) and investigate the association between use of β-blockers at discharge and mortality in patients with COPD.

Methods: We studied 1530 patients. The association of COPD with mortality was examined in adjusted Fine-Gray proportional hazard models where heart transplantation and ventricular assist device implantation were treated as competing risks. The primary outcome was 5-year all-cause mortality.

Results: After adjusting for establisked risk markers, the subdistribution hazard ratios (SHR) of 5-year mortality for COPD patients compared with non-COPD patients was 1.25 (95% confidence intervals [CIs] 1.06–1.47; p = .007). The relative risk of death for COPD patients increased steeply from 30 to 180 days, and remained noticeably high throughout the entire follow-up. Among patients with comorbid COPD, the use of β-blockers at discharge was associated with a significantly reduced risk of 1-year post-discharge mortality (SHR 0.66, 95%CIs 0.53–0.83; p ≤.001).

Conclusions: Our data indicate that ADHF patients with comorbid COPD have a worse long-term survival than those without comorbid COPD. Most of the excess mortality occurred in the first few months following hospitalization. Our data also suggest that the use of β-blockers at discharge is independently associated with improved survival in ADHF patients with COPD.

1. Introduction

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are recognized worldwide as major healthcare burdens for their growing prevalence and impact on healthcare systems. It is estimated that HF afflicts > 61 million people around the world and > 6 million in either the United States or Europe [1–3]. The prevalence of HF is estimated at about 2% in adults, rising to 10% in the elderly. The epidemiological burden of COPD is even heavier. Based on a meta–regression epidemiological model, Adeloye et al. estimated about 384 million COPD cases worldwide and 66 million in Europe in the year 2010 among people aged 30 years or more, corresponding to a prevalence of 11.7% and 13.7%, respectively [4]. Primarily because of demographic changes, the prevalence of HF and COPD is expected to rise in the next few decades.

Both HF and COPD are leading causes of morbidity, mortality and disability [1,2]. Heart failure is the most common cause of hospitalization for adults. > 1 million hospitalizations occur annually in either the United States or Europe, with the majority of patients being admitted to internal medicine wards [5–10]. Among acute HF syndromes, acute decompensation of chronic HF (ADHF) is the most common clinical presentation [5–7]. Hospitalized HF still has an ominous prognosis. Twenty five percent to 35% of the patients die within one year of discharge [9–12]. COPD is among the most common comorbidities in patients hospitalized with HF, with a reported prevalence ranging from 10% to 41% [13,14]. On the other hand, the prevalence of HF in COPD patients ranges from 20% to 70% [15]. It is noteworthy that 14% of elderly patients hospitalized for HF receive concurrent treatments for exacerbation of COPD, while 19% of those hospitalized with COPD receive concurrent treatments for acute HF [16]. Although

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COPD is generally recognized to be associated with poorer outcomes in patients admitted with acute HF, the results of previous studies with regard to increased mortality and risk trajectories were not univocal [17–36]. Differences in diagnostic criteria for COPD, time-horizon of risk assessment, and number and type of variables adjusted for in multivariable modeling may have contributed to between-study differences. An additional, remarkable finding is that recommended therapies are underused in HF patients with comorbid COPD [37]. Moreover, HF patients with comorbid COPD may be less likely to undergo heart transplantation (HT) and ventricular assist device implantation (VADi) compared with their counterparts without COPD. Both HT and VADi represent important competing events as they can fundamentally alter the probability of the occurrence of death. Failure to account for these competing events may result in overestimation of the absolute mortality risk [38,39]. Unfortunately, most previous studies comparing mortality in HF patients with or without comorbid COPD did not report the proportion of patients who underwent HT/VADi. These findings underscore the challenges in addressing comorbid COPD in acute HF. The aim of this study was two-fold: 1) to assess the long-term prognostic impact of COPD in patients admitted for ADHF, accounting for the competing risks of HT and VADi; 2) to investigate the association between use of renin-angiotensin-aldosterone system inhibitors (RAASI) and β-blockers at discharge and mortality in ADHF patients with comorbid COPD.

2. Methods

The study population consisted of 1595 patients admitted to the cardiology wards of the Niguarda Hospital (Milan) and the Maugeri Institutes of Cassano Murge (Bari) and Tradate (Varese) for ADHF. Enrollment period varied among the centers but ran from January 2006 to July 2016 overall. We identified the patients discharged with a primary diagnosis of HF (International Classification of Diseases, Ninth Revision [ICD-9] codes 428.0–428.4) using a computer-generated list obtained from our administrative database. Once these patients were identified, those fulfilling the selection criteria were selected by reviewing medical records and hospital discharge letters in our electronic Hospital Information Systems. Patients were included according to the following criteria: current hospitalization for ADHF, history of HF of at least 1 year, and chronic treatment with standard therapies. Exclusion criteria were: “de novo” acute HF; cardiogenic shock; acute HF developed after admission for another admitting diagnosis or due to acute myocarditis or restrictive cardiomyopathy; acute coronary syndromes or angina pectoris; recent (< 3 months) cardiac surgical or percutaneous procedures; planned coronary revascularization; congenital heart disease; stenotic valvular disease. Chronic obstructive pulmonary disease was diagnosed based on patient's medical records documenting a past diagnosis of COPD, chronic medication use for COPD, and/or previous hospitalizations for exacerbation of COPD. The Institutional Review Board approved the study. Patients' data were deidentified. The primary outcome of interest was all-cause mortality within 5 years after admission.

3. Data collection

Information on demographics, medical history, presenting clinical characteristics, laboratory data at admission, echocardiographic findings, and discharge medications were retrieved from the hospital electronic information system at each participating center. Outcome status was ascertained by linking with the Health Regional Information System, by interviewing patients, their relatives, and/or their treating physician, or by direct knowledge.

3.1. Statistical analysis

Data are reported as mean and standard deviation (SD) or median with 25th and 75th percentiles for continuous variables or percentage for categorical variables. We used the Student's *t*-test or the Mann-Whitney test to compare continuous variables and the χ^2 test to compare categorical variables.

The absolute risk of death was estimated using the Cumulative Incidence Function (CIF) method [38,39]. Compared with naïve Kaplan-Meier method where competing events are treated as censored observations, the CIF method allows accounting for competing risks. We used the CIF curves to illustrate the different outcomes of death, HT/VADi, and survival free of HT/VAD for COPD and non-COPD patients. Median HT/VAD-free survival time was calculated as the shortest survival time for which the survivor function is ≤ 0.5. For purposes of comparison, naïve Kaplan-Meier mortality curves were constructed. In this analysis, the patients who underwent HT or VADi during follow-up were censored at the time of the event. The association of COPD with mortality was examined in unadjusted and adjusted Fine-Gray proportional hazard models where HT and VADi were considered to be competing risks. The subdistribution hazard ratios (SHR) with 95% confidence intervals (CI) for death were calculated. The model incorporated age, sex, diabetes mellitus, HF-related hospitalizations in the 6 months preceding the index event, symptoms severity at admission, admission systolic blood pressure, use of inotropes during hospitalization, left ventricular ejection fraction (LVEF), and admission estimated glomerular filtration rate (eGFR), NT-proBNP, hemoglobin, and sodium levels as covariates. Sex was forced into the model. These covariates were chosen a priori based on clinical relevance or consistent association with mortality in previous studies [40–42]. To characterize the extent to which the risk of death was higher among COPD patients compared to non-COPD patients, we calculated the relative risk of death for patients with COPD at 30-day time-intervals until the 180th day from admission and at 90-day time-intervals thereafter [12]. For this purpose, we used the cumulative incidence of death estimated by the CIF method. Moreover, we identified the covariates associated with use of β-blockers at discharge using multivariable logistic regression analysis. Odds ratios (OR) with 95% Cis were calculated. Finally, we examined the association of the use of β-blockers and the combined treatment with a RAASI and a β-blocker at discharge with 1-year post-discharge mortality among patients with comorbid COPD using Fine-Gray proportional hazard models adjusted for the above-mentioned prognostic covariates.

4. Results

Of the 1595 patients, 12 were excluded because of missing data for admission systolic blood pressure and 37 because of unavailable LVEF. Sixteen patients were lost to follow-up. Thus, 1530 patients were available for analysis. Table 1 shows the baseline characteristics of the patients. Compared with non-COPD patients, those with COPD were older and more frequently males, and had higher body mass index, more comorbidities, higher LVEF, more severe symptoms, and higher systolic blood pressure and poorer renal function at admission.

4.1. Outcomes

During the follow-up, 701 patients died and 158 underwent HT/VADi. Fig. 1 shows the CIF curves for HT/VAD-free survival, mortality, and HT/VADi in the overall cohort and in patients stratified by the presence of comorbid COPD. Patients with or without comorbid COPD had comparable 30-day mortality (5.8% vs 5.6%). The 5-year mortality was 62.1% in the entire cohort, 73.3% among COPD patients, and 58.3% among non-COPD patients. The median HT/VAD-free survival time was 614 days in the entire cohort, 633 in patients without COPD and 554 in those with COPD. The 5-year incidence of HT/VADi was 4.2% among COPD patients and 15.7% among non-COPD patients. Compared with the CIF method, naïve Kaplan-Meier method overestimated 5-year mortality by 15% in non-COPD patients (66.9% vs

Table 1
Baseline characteristics stratified by the presence of COPD.

	All (N = 1530)	No COPD (N = 1134)	COPD (N = 396)	p value
Age (years), mean (SD)	69 (14)	67 (14)	74 (11)	< 0.001
> 75 years, %	36.7	31.6	51.4	< 0.001
Males, %	71.5	70.0	75.7	0.032
Body mass index (Kg/m^2), mean (SD) *	27 (6)	27 (6)	28 (6)	0.005
Comorbidities				
Hypertension, %	53.3	49.6	64.1	< 0.001
Diabetes, %	32.5	31.9	34.2	0.404
Previous CVE, %	9.7	9.7	9.6	0.967
Known thyroid disease, %	19.8	20.5	17.7	0.228
Hypothyroidism, %	15.4	15.9	14.2	0.425
Hyperthyroidism, %	4.4	4.7	3.5	0.347
Known liver disease, %	7.6	8.2	6.1	0.173
Ischemic heart disease, %	45.4	43.3	51.6	0.004
Previous CABG/PTCA, %	34.7	32.9	40.0	0.010
Atrial fibrillation, %	43.1	41.0	49.4	0.004
Clinical and laboratory findings				
HF-related hospitalizations < 6 months, %	43.7	43.3	44.6	0.676
On waiting list for heart transplantation, %	8.8	10.7	3.3	< 0.001
ICD, %	51.3	54.6	41.8	< 0.001
ICD + CRT, %	22.4	23.5	19.2	0.079
Dyspnea at rest/orthopnea at admission, %	34.1	31.8	40.8	0.001
Treatment with inotropes, %	26.2	27.8	21.5	0.014
Systolic blood pressure (mmHg), mean (SD)	115 (22)	113 (22)	118 (21)	< 0.001
Systolic blood pressure < 100 mmHg, %	20.3	23.1	12.2	< 0.001
Serum creatinine (mg/dL), mean (SD)	1.49 (0.73)	1.48 (0.75)	1.50 (0.65)	0.700
eGFR (mL/min/1.73m^2), mean (SD)	55 (24)	56 (25)	52 (22)	0.013
eGFR < 60 mL/min/1.73m^2, %	60.1	58.4	65.1	0.020
eGFR 45 to 60, %	23.7	23.4	24.3	–
eGFR 30 to 44, %	21.6	19.7	27.1	–
eGFR 15 to 30, %	13.1	13.5	11.9	–
eGFR < 15, %	1.8	1.8	1.8	–
NT-proBNP (pg/mL), median (IQR)	4284 (1961–9380)	4372 (2068–9382)	3949 (1760–9311)	0.869
Serum sodium (mmol/l), mean (SD)	138.6 (4.6)	138.5 (4.6)	138.9 (4.6)	0.129
Serum sodium < 136 mmol/L, %	21.9	22.4	20.5	0.438
Serum potassium (mmol/L), mean (SD)	4.27 (0.55)	4.26 (0.55)	4.32 (0.55)	0.065
Hemoglobin (g/dL), Mean (SD)	12.3 (2.0)	12.3 (2.0)	12.3 (2.0)	0.825
Anemia (< 13 mg/dL in men, < 12 mg/dL in women), %	55.4	55.1	56.2	0.696
Total cholesterol (mg/dL), mean (SD)	143 (42)	142 (42)	146 (42)	0.274
LVEF, mean (SD)	32 (12)	31 (12)	35 (13)	< 0.001
LVEF ≤40%, %	78.8	81.6	70.6	< 0.001
Severe mitral regurgitation, %	7.1	7.3	6.3	0.511
Severe tricuspid regurgitation, %	7.4	7.4	7.3	0.969

Abbreviations: COPD denotes chronic obstructive pulmonary disease, CABG coronary artery bypass graft, PTCA percutaneous coronary angioplasty, ICD implantable cardioverter defibrillator, CRT cardiac resynchronization therapy, eGFR estimated glomerular filtration rate, LVEF left ventricular ejection fraction, SD standard deviation, IQR interquartile range.

58.3%) and by 4% in COPD patients (76.1% vs 73.3%).

The relative risk of death for COPD patients compared with non-COPD patients increased steeply from 30 to 180 days, and remained noticeably high throughout the entire follow-up (Fig. 2).

Table 2 shows the results of the Fine-Gray multivariable analysis. Age, diabetes, previous hospitalizations, dyspnea at rest/orthopnea at presentation, admission systolic blood pressure, LVEF, and admission NT-proBNP, eGFR, hemoglobin, and sodium levels were independently associated with 5-year mortality risk. After full adjustment in multivariable model, the SHR of death at 5 years for COPD patients was 1.25 (95% CIs 1.06–1.47; p = .007).

4.2. Treatment at discharge

Use of RAASIs and β-blockers at discharge is reported in Table 3. Either RAAS-Is or β-blockers were significantly underused in COPD patients compared with non-COPD patients. Among COPD patients, bisoprolol was the most frequently prescribed β-blocker. After restricting the sample to the subgroup with reduced LVEF, the difference in the frequency of β-blocker prescription remained statistically significant (p < .001). Combined treatment with a RAASI and a β-blocker was prescribed to 61.1% of the non-COPD patients and 41.6% of the COPD patients (p < .001). The corresponding figures for patients with reduced LVEF were 65.0% and 46.6% (p < .001), respectively.

Increasing age (OR 0.77 [95% CIs 0.66–0.89], p = .020), COPD (OR 0.45 [95% CIs 0.34–0.59], p < .001), severe dyspnea at admission (OR 0.65 [95% CIs 0.49–0.86], p = .002), and increasing LVEF (OR 0.90 [95% CIs 0.85–0.96], p < .001) were independently associated with reduced probability of β-blocker use at discharge (Table 4).

After full adjustment for prognostic covariates, the use of β-blockers and the combined treatment with a RAAS-I plus a β-blocker at discharge was associated with a 34% (SHR 0.66, 95% CIs 0.53–0.83; p ≤.001) and 39% (SHR 0.61, 95% CIs 0.50–0.76; p < .001) reduced risk for 1-year post-discharge mortality, respectively. After restricting the sample to the subgroup with COPD, the corresponding SHR were 0.55 (95% 0.37–0.80; p = .002) and 0.40 (95% 0.25–0.62; p < .001), respectively. Fig. 3A and B shows the CIF curves for 1-year post-discharge mortality in patients with comorbid COPD who were prescribed a β-blocker or the combined treatment with a RAAS-I and a β-blocker at discharge compared with those who did not. There was no difference in the magnitude of the beneficial effect of β-blockers when the patients with comorbid COPD were stratified according to the presence of atrial fibrillation or LVEF > or ≤ 0.40 (Supplementary Fig. 1).

Among COPD patients, the adjusted SHR of 1-year mortality for those discharged on bisoprolol or carvedilol was 0.47 (95% CIs 0.32–0.69; p < .001) and 0.59 (95% CIs 0.36–0.99; p = .044),

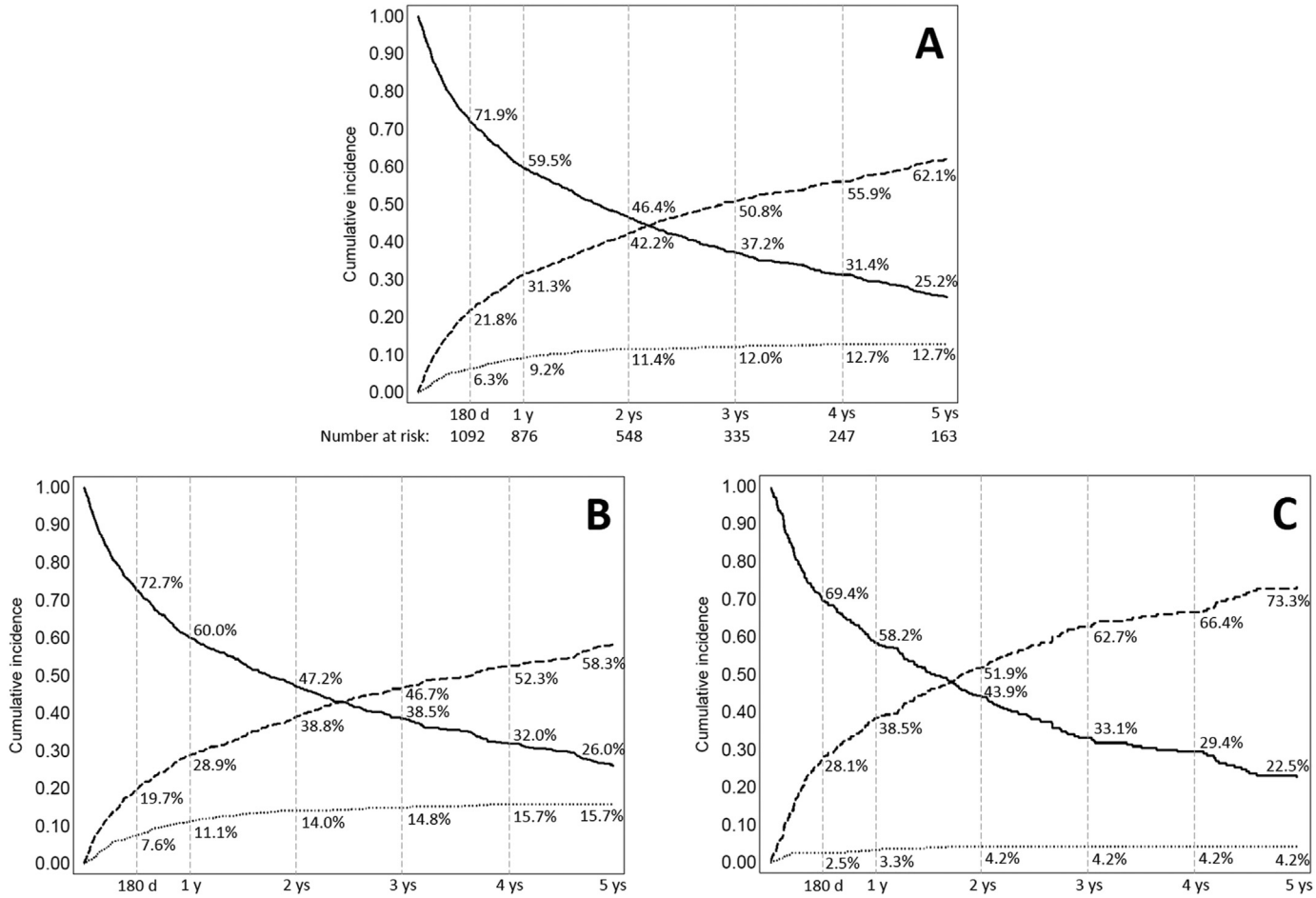

Fig. 1. Cumulative incidence curves for heart transplantation/ventricular assist device implantation-free survival, mortality, and, heart transplantation/ventricular assist device implantation in all patients (A) and in those without (B) or with comorbid COPD (C). Solid line indicates heart transplantation/ventricular assist device implantation-free survival, dashed lines mortality, and dotted lines the incidence of heart transplantation/ventricular assist device implantation. Numbers in brackets denote the estimated incidence.

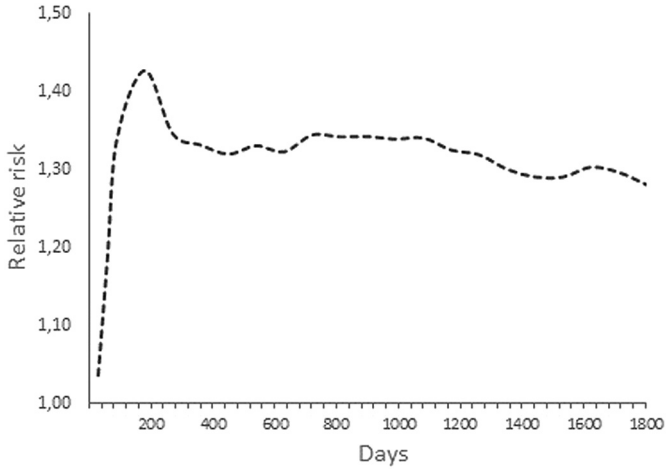

Fig. 2. Relative risk of death for patients with COPD.

Table 2
Results of the Fine-Gray multivariable analysis.

	SHR (95% CIs)	P value
Age (per 5-year increase above 65 years)	1.35 (1.28–1.43)	< 0.001
Male sex	1.00 (0.85–1.19)	0.961
Diabetes mellitus	1.25 (1.07–1.46)	0.006
HF hospitalizations < 6 months	1.20 (1.03–1.39)	0.017
Dyspnea at rest/orthopnea at admission	1.31 (1.13–1.52)	< 0.001
Systolic blood pressure (per 10-unit increase)	0.93 (0.89–0.96)	< 0.001
Treatment with inotropes	1.08 (0.88–1.31)	0.458
LVEF (per 5-point decrease below 0.40)	1.08 (1.01–1.14)	0.016
eGFR (per 5 mL-decrease below 60 mL/min/ 1.73m^2)	1.05 (1.02–1.08)	< 0.001
Log NT-proBNP	1.28 (1.18–1.38)	< 0.001
Hemoglobin (per 1 g-decrease below 13 g/dL in men and 12 g/dL in women)	1.14 (1.07–1.22)	< 0.001
Serum sodium < 136 mmol/L	1.25 (1.04–1.51)	0.019

Abbreviations: SHR denotes subdistribution hazard ratios, LVEF denotes left ventricular ejection fraction, eGFR estimated glomerular filtration rate.

respectively.

5. Discussion

The major findings of the study are: 1) COPD was associated with increased long-term mortality in patients admitted for acute decompensated HF; 2) 30-day mortality among COPD and non-COPD patients was comparable; however, the relative risk of death for patients with COPD increased steeply from 30 to 180 days after admission and tended to plateau thereafter; 3) use of β-blockers at discharge was associated with improved 1-year post-discharge survival in patients with comorbid COPD.

The results of previous studies investigating the effect of COPD on mortality were not univocal [17–36] (Supplementary Table 1).

Table 3
Prescribed treatments at discharge.

	All (N = 1407)	No COPD (N = 1042)	COPD (N = 365)	p value
RAAS-Is. %	70.9	72.9	65.2	0.006
≥ 50% of the target dose, % [a]	38.5	36.2	45.8	0.134
Angiotensin-converting-enzyme inhibitors, % [a]	76.3	77.6	71.8	
Angiotensin II receptor antagonists, % [a]	23.7	22.4	28.2	
B-blockers, %	77.8	82.7	63.8	< 0.001
≥ 50% of the target dose, % [a]	24.9	26.1	20.6	0.088
Bisoprolol, % [a]	53.1	49.4	70.8	
Carvedilol, % [a]	40.2	44.0	21.9	
Metoprolol, % [a]	2.1	2.2	1.7	
Nebivolol, % [a]	2.8	2.3	4.7	
Others, % [a]	1.8	2.1	0.9	
RAAS-I plus β-blocker, %	56.1	61.1	41.6	< 0.001
Furosemide, %	98.2	98.0	98.6	0.647
Mineralocorticoid receptor antagonists, %	66.0	67.0	63.3	0.222

Left ventricular ejection fraction ≤ 0.40

	All patients (N. 1093)	No COPD (N. 840)	COPD (N. 253)	p value
RAAS-Is, %	74	75.2	70	0.102
≥ 50% of the target dose, % [a]	35.8	34.7	40.1	0.184
B-blockers, %	81.3	85.4	68	< 0.001
≥ 50% of the target dose, % [a]	24.3	25.5	19.2	0.092
RAAS-I plus β-blocker, %	60.7	65.0	46.6	< 0.001

Abbreviations: COPD denotes chronic obstructive pulmonary disease, RAASI renin-angiotensin-aldosterone system inhibitor.
[a] Percentages are referred to the number of patients who were prescribed RAASi or β-blockers.

Moreover, comparative evaluation of the results suggests a remarkable between-study heterogeneity in risk trajectories. While some studies found that the prognostic impact of COPD on mortality in acute HF patients runs out within few months after admission [19,20,32], other studies suggested that most of the prognostic impact of COPD takes place in the long-term [25,31] (Supplementary Table 1). In the present study, comorbid COPD was independently associated with 25% increased risk of death at 5 years. The absolute risk of death at 5 years was 73.3% in COPD and 58.3% in non-COPD patients. Nearly 13% of the patients underwent HT or VADi during the follow-up, with COPD patients being almost 4-times less likely to undergo such advanced treatments than non-COPD patients were (4.2% vs 15.7%). Heart transplantation and VADi represent important competing risks in HF as they fundamentally alter the probability of the occurrence of death. Careful attention to the method of analysis has been recommended in the presence of competing risks, especially when the absolute percentage of competing events exceeds 10% [39]. Since naïve Kaplan-Meier method may overestimate the absolute mortality risk in the presence of competing risks, we used the CIF method to estimate absolute mortality risks [39]. Remarkably, the Kaplan-Meier method overestimated the absolute risk of death at 5 years by 15% in non-COPD and 4% in COPD patients, resulting in a reduced difference in mortality between COPD and non-COPD patients.

There was no difference in 30-day mortality between patients with or without comorbid COPD. However, the relative risk of death for COPD compared with non-COPD patients increased steeply from 30 to 180 days and remained noticeably high thereafter, suggesting that most of the excess mortality among patients with comorbid COPD occurs in the first few months after hospitalization. However, clinical progression of COPD toward more severe stages of disease might contribute to increased late mortality among patients with comorbid COPD. Approximately 20% of the patients with COPD, indeed, present accelerated disease progression irrespective of the initial Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage and medication

Table 4
Predictors of β-blockers use at discharge.

	Univariate analysis		Multivariable analysis	
	Odds ratio (95% CIs)	p value	Odds ratio (95% CIs)	p value
Age (per 5-year increase above 65 years)	0.77 (0.66–0.89)	< 0.001	0.87 (0.77–0.98)	0.020
Male sex	0.86 (0.63–1.19)	0.366		
COPD	0.46 (0.34–0.61)	< 0.001	0.45 (0.34–0.59)	< 0.001
Hypertension	1.08 (0.80–1.46)	0.615		
Diabetes	0.90 (0.67–1.20)	0.477		
Ischemic heart disease	1.33 (0.99–1.78)	0.055		
Atrial fibrillation	1.22 (0.92–1.62)	0.171		
HF-related hospitalizations < 6 months	0.82 (0.62–1.08)	0.161		
Dyspnea at rest/orthopnea at admission	0.67 (0.50–0.89)	0.005	0.65 (0.49–0.86)	0.002
Treatment with inotropes	0.79 (0.55–1.14)	0.212		
Systolic blood pressure (per 10-unit increase)	1.02 (0.96–1.09)	0.524		
Log NT-proBNP (pg/ml)	1.13 (0.98–1.29)	0.083		
eGFR (per 5 mL-decrease below 60 mL/min/1.73m^2)	0.99 (0.92–1.05)	0.686		
LVEF (per 5-unit increase)	0.90 (0.84–0.97)	0.004	0.90 (0.85–0.96)	< 0.001

Abbreviations: CI denotes confidence intervals, COPD chronic obstructive pulmonary disease, eGFR estimated glomerular filtration rate, LVEF: left ventricular ejection fraction.

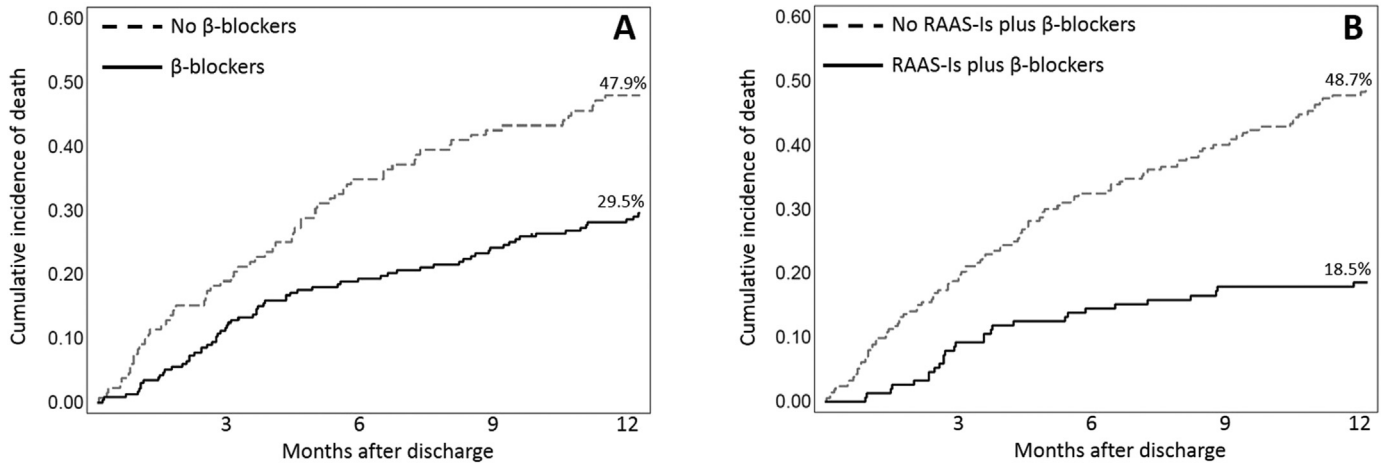

Fig. 3. Cumulative incidence curves for mortality in patients with comorbid COPD stratified according to the use of β-blockers (A) or the use of the combined treatment with a RAAS-I plus a β-blocker (B) at discharge.

treatment [43].

Remarkably, our data also suggest that low systolic blood pressure, renal dysfunction, increasing NT-proBNP concentrations, and hyponatremia, which are regarded as the most powerful predictors of short- and mid-term mortality in acute HF, also predict long-term mortality.

It is now ten years since the European Society of Cardiology guidelines stated that COPD "is not a contra-indication" to β-blocker treatment in HF [9,44]. In 2013, the GOLD guidelines stated that the benefits of treatment with cardioselective β-blockers in HF "clearly outweigh any potential risk associated with treatment even in patients with severe COPD" [45]. Nonetheless, multiple studies have documented that a treatment gap still exists worldwide [19,20,46]. This study is not an exception. After multivariable adjustment, the patients with comorbid COPD were 55% less likely to be prescribed β-blockers at discharge than those without COPD. The gap persisted even when the analysis was restricted to the patient subgroup with reduced LVEF. Chronic obstructive pulmonary disease, however, was not the only factor for underuse of β-blockers. Symptoms severity at admission, advanced age, and increasing LVEF significantly contributed, suggesting that these factors should be accounted for in future studies addressing the use of β-blockers at discharge in hospitalized patients [47]. Patients with comorbid COPD also were less likely to be discharged on combined treatment with a β-blocker and a RAASIs compared with non-COPD patients (41.6% vs 61.1%). Our data are comparable with those reported in previous studies. In the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry, β-blockers were prescribed to 65.9% of hospitalized HF patients with and 75.4% of those without comorbid COPD [19]. Similarly, in the European Society of Cardiology Heart Failure Long-Term Registry, β-blockers were prescribed to 62.8% of the hospitalized HF patients with COPD compared with 76.9% of non-COPD patients [20]. Notably, < 10% of the patients were judged to have true contra-indications to β-blocker treatment [20], a value consistent with other published reports [48]. In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome (EVEREST) study, 63% of the COPD patients received β-blockers at discharge, compared with 71.1% of non-COPD patients [18]. In two other studies, however, prescription of β-blockers was definitely lower [17,31]. Finally, in the large study of Lipworth et al., HF patients with comorbid COPD were 46% less likely to be treated with a β-blocker in conjunction with a RAASI compared with patients with HF only [37].

Our data also suggest that use of β-blockers at discharge is associated with improved survival in HF patients with comorbid COPD. After adjustment for established markers of risk, one-year post-discharge mortality was 45% lower in COPD patients who were prescribed a β-blocker compared with those who were not. The magnitude of relative risk reduction was even larger (60%) when β-blockers were prescribed in combination with a RAASI. The beneficial effect of β-blockers was apparent regardless of the presence of atrial fibrillation or whether LVEF was ≤40% or > 40%, though the limited number of events in the subgroup with LVEF > 0.40 resulted in wide confidence intervals. This finding is consistent with previous observational studies documenting that the use of β-blockers is associated with lower risk of all-cause mortality in HF patients with preserved LVEF [49–53]. Our findings support the concept that patients with acute HF and comorbid COPD should not be denied β-blocker treatment at discharge. Concerns regarding potential bronchoconstriction remain the main reason for underutilization of β-blockers in HF patients with comorbid COPD [20,54]. However, there is compelling evidence that β-blockers proven beneficial in HF, including carvedilol, are safe and well-tolerated in patients with COPD [55–58].

6. Strengths and limitations

This study has both strengths and limitations. Strengths include the analytical approach used to estimate the absolute mortality risk and evaluate the association between COPD and risk of death and the time horizon of risk assessment. According to Austin et al. [39], failure to account for competing risks can result in "overestimation of the probability of the occurrence of the event of interest and mis-estimation of the magnitude of relative effects of covariates on the incidence of the outcome". Long-term follow-up may reveal important outcome differences between groups, provide information regarding residual lifetime, and help informing decision-making. Some limitations should be acknowledged. This was a retrospective study. Other unmeasured or not documented factors may have influenced outcome. As with previous studies, the diagnosis of COPD was based on clinical criteria, not on pulmonary function testing. According to current GOLD guidelines, spirometry is required to confirm the diagnosis of COPD [59]. However, using spirometry to diagnose COPD in acute HF may result in misleading results due to HF-induced abnormalities in respiratory function [60]. We were unable to determine whether increased mortality in COPD patients was due to cardiovascular or non-cardiovascular causes. However, it is well known the adjudication of the mode of death is unreliable in observational studies. Although we adjusted for established risk markers to assess the association between risk of death and use of β-blockers at discharge, a "prescribing bias" cannot be excluded [61]. As with previous studies, we had no data on possible treatment changes after hospitalization. To address this potential bias, we restricted the analysis of the relationship between mortality and use of

recommended therapies to the first year after discharge. Previous data suggest that evidence-based therapies prescribed at discharge seldom are stopped in the subsequent months [46]. In addition, there is robust evidence that β-blockers are well tolerated in patients with COPD [55,56].

7. Conclusions

In conclusion, our data indicate that patients admitted for ADHF with comorbid COPD have a definitely worse survival in the long-term compared with patients without comorbid COPD. Most of the excess mortality in patients with comorbid COPD occurred in the first few months following hospitalization. Our data also suggest that use of β-blockers at discharge is independently associated with reduced mortality risk in patients with comorbid COPD.

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Conflict of interest

None declared

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