

Impact of Chronic Obstructive Pulmonary Disease on Long-Term Outcome of Patients Hospitalized for Heart Failure

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Chronic obstructive pulmonary disease (COPD) is a frequently neglected co-morbidity in patients with heart failure (HF). The aim of this study was to evaluate the prognostic impact of COPD in patients hospitalized for HF. Consecutive patients (n = 799) admitted for a first episode of HF in all healthcare establishments of the Somme department (France) during 2000 were prospectively enrolled. Baseline characteristics and long-term prognosis were compared according to COPD status. COPD was diagnosed in 156 patients (19.5%). Compared with the no-COPD group, patients with COPD were predominantly men, more often smokers, and had lower discharge prescription rates of β blockers (6% vs 27%, $p < 0.001$). Five-year survival rate in patients with COPD was significantly lower than that of the no-COPD group (31% vs 42%, $p = 0.03$). Compared with the expected survival of the age- and gender-matched general population, the 5-year survival rate in patients with COPD was dramatically lower (31% vs 71%). On multivariable analysis, COPD was a strong predictor of poorer outcome (hazard ratio 1.53, 95% confidence interval 1.21 to 1.94, $p < 0.001$). COPD was an independent predictor of mortality in patients with preserved left ventricular ejection fraction and in patients with reduced ejection fraction. In conclusion, patients with HF and associated COPD have a poor prognosis with an impressive excess mortality compared to HF patients without COPD and the general population. Beta-blocker prescription rates remain deceptively low in this category of patients with HF. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101:353–358)

Noncardiac co-morbidities are frequent in patients with heart failure (HF) and have an adverse impact on mortality and hospital readmissions.¹ Chronic obstructive pulmonary disease (COPD) is a frequently neglected co-morbidity in patients with HF.^{2–4} It complicates the diagnostic assessment of patients with suspected HF and influences the choice of medical therapy. Recent reports have suggested that patients with COPD are at increased risk for hospitalization and death due to cardiovascular diseases, including HF.^{5,6} Several factors can explain the association between COPD and cardiovascular diseases, including shared risk factors and factors that increase stress on the cardiovascular system or precipitate arrhythmic events. Data on the prognostic impact of COPD in patients with HF are scarce and mostly derived from retrospective analyses with relatively short follow-up^{2,7–9} or selected populations in clinical trial settings.¹⁰ To our knowledge, no study has specifically assessed the implications of co-morbid COPD on the long-term prognosis of patients with HF. The aims of the present prospective study including consecutive patients hospitalized for a first episode of HF were to determine the clinical

features and treatment of patients with HF and COPD and assess the prognostic impact of COPD in patients with HF.

Methods

The Somme is a department of France with a population of 555,551 inhabitants, according to the 1999 census. The Somme department has 11 healthcare establishments, managing patients with HF: 1 university hospital, 7 general hospitals, 2 private clinics, and 1 medium and long-stay unit. General practitioners, cardiologists, and internal physicians of these centers agreed to participate in this study.

Consecutive patients >20 years old hospitalized for a first episode of HF in any of these establishments during 2000 were prospectively enrolled. The diagnosis of HF was made by the attending physician based on history, symptoms, physical signs, and chest x-ray on admission. During the index hospitalization 2 cardiologists specifically recruited for this purpose, reviewed all medical records to validate the diagnosis of HF according to the Framingham criteria amended by the European Society of Cardiology.¹¹ The diagnosis was not validated in 12 of the 811 enrolled patients. The study population therefore comprised 799 patients (410 men and 389 women).

Clinical data including medical history, cardiovascular risk factors, and results of complementary investigations (laboratory tests, electrocardiogram, chest x-ray on admission, echocardiography) were recorded on individual case report forms. Ejection fraction (EF) was determined during hospitalization by echocardiography (n = 648) and/or left ventriculography (n = 103). Echocardiograms were re-

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Table 1
Baseline clinical characteristics according to presence or absence of chronic obstructive pulmonary disease

Variables	COPD		p Value
	Yes (n = 156)	No (n = 643)	
Demographics and medical history			
Age (yrs)	74.9 ± 10.9	75.6 ± 12.2	0.51
Women	40 (25.6%)	349 (54.3%)	<0.001
Smoker	107 (68.6%)	176 (27.4%)	<0.001
Systolic blood pressure (mm Hg)	145.7 ± 29.5	149.1 ± 31.5	0.21
Diastolic blood pressure (mm Hg)	79.3 ± 16.3	81.2 ± 16.9	0.22
NYHA classes III–IV on admission	148 (94.9%)	614 (95.5%)	0.74
Diabetes mellitus	32 (20.5%)	164 (25.5%)	0.19
Stroke	8 (5.1%)	37 (5.8%)	0.76
Cancer	12 (7.7%)	73 (11.4%)	0.18
Etiology of HF			
Hypertension	54 (34.6%)	223 (34.7%)	0.99
Coronary heart disease	60 (38.5%)	242 (37.6%)	0.85
Valvular disease	10 (6.4%)	62 (9.6%)	0.21
Idiopathic dilated cardiomyopathy	18 (11.5%)	64 (10.0%)	0.56
Other and unknown	23 (9%)	52 (8%)	0.34
Electrocardiogram on admission			
Atrial fibrillation	53 (34.0%)	211 (32.8%)	0.78
Pathologic Q wave	26 (16.7%)	81 (12.6%)	0.18
Left bundle branch block	21 (13.5%)	88 (13.7%)	0.94
Left ventricular hypertrophy	25 (16.0%)	111 (17.3%)	0.71
Chest x-ray data			
Cardiomegaly	111 (71.2%)	449 (69.9%)	0.77
Echocardiography data			
Left ventricular end-diastolic diameter (mm)	54.7 ± 8.8	54.3 ± 9.4	0.69
Left ventricular end-systolic diameter (mm)	38.9 ± 9.9	39.2 ± 10.9	0.79
Left ventricular ejection fraction (%)	50.4 ± 15.6	50.4 ± 16.0	0.98
Left ventricular ejection fraction ≥50%	61 (44.9%)	233 (44.3%)	0.91
Left atrial diameter (mm)	42.1 ± 6.9	41.8 ± 7.3	0.74
Systolic pulmonary pressure (mm Hg)	41.0 ± 12.5	42.8 ± 11.9	0.31
Laboratory data			
Creatinine clearance (ml/min/1.73 m ²)	61.3 ± 22.7	57.8 ± 24.0	0.10
Sodium (mEq/L)	137.3 ± 4.6	137.3 ± 4.7	0.96
Hemoglobin (g/dl)	13.5 ± 2.2	13.2 ± 2.0	0.90

NYHA = New York Heart Association.

corded according to the guidelines of the American Society of Echocardiography.¹² When >1 method was performed, an average EF was calculated. An EF ≥50% was used to define HF with preserved ejection fraction.¹³ An assessment of the EF was available in 83% of patients. The diagnosis of COPD was previously made by internists or chest physicians and obtained from medical records. If information relied only on the patient, use of specific inhalation or oral COPD medication was required. An estimate of the glomerular filtration rate on admission was calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula including age, race, gender, and serum creatinine.¹⁴

Medical treatment records were completed at discharge and at 1, 3, and 5 years. Prescription of the main therapeutic classes in HF was recorded.

One-, 3-, and 5-year overall mortality rates after admission were determined. The vital status at 1, 3, and 5 years was obtained either by a consultation with the general practitioner or the referring cardiologist or by consulting the civil registry. No patient was lost to follow-up at 1 and 3 years. Five patients (0.6%) were lost to follow-up at 5 years.

Continuous variables were expressed as mean ± SD and were compared between groups by Student's *t* test. Categorical variables were summarized by frequency percents and analyzed by chi-square test. Multivariable relative risks were determined using proportional hazard models in a backward stepwise regression analysis. A predefined model was used including covariates of potential prognostic impact (age, gender, smoking, ischemic etiology, hypertensive etiology, COPD, diabetes mellitus, stroke, cancer, atrial fibrillation, serum sodium, creatinine clearance, hemoglobin, and EF). Age, serum sodium, creatinine clearance, hemoglobin, and EF were entered in the models as continuous variables. Adjusted survival curves were constructed after adjustment for all covariates in the model. A separate multivariable model was carried out in survivors to the index hospitalization with adjustment for treatment on discharge (β blockers, angiotensin-converting enzyme [ACE] inhibitors, loop diuretics, and calcium channel blockers).

Survival for the 2 groups (COPD and no-COPD) was estimated by the Kaplan-Meier method. Differences in time-to-death between groups were analyzed using a

Table 2
Medical treatment at discharge and during follow-up according to chronic obstructive pulmonary disease (COPD) status

Drug	Discharge			1 year			3 years			5 years		
	COPD	No COPD	p Value	COPD	No COPD	p Value	COPD	No COPD	p Value	COPD	No COPD	p Value
ACE inhibitor	71 (48.0%)	330 (56.0%)	0.07	60 (54.1%)	257 (56.4%)	0.66	33 (49.3%)	180 (53.4%)	0.53	21 (45.7%)	121 (48.8%)	0.69
β Blocker	9 (6.1%)	159 (27.1%)	<0.001	11 (9.9%)	167 (36.5%)	<0.001	5 (7.5%)	138 (40.8%)	<0.001	3 (6.5%)	121 (48.8%)	<0.001
Loop diuretic	139 (93.9%)	517 (88.1%)	0.04	105 (94.6%)	388 (85.1%)	0.008	54 (80.6%)	257 (76.3%)	0.44	37 (80.4%)	178 (71.8%)	0.22
Aldosterone receptor antagonist	38 (25.7%)	145 (24.7%)	0.81	34 (30.6%)	132 (28.9%)	0.73	16 (23.9%)	85 (25.1%)	0.83	10 (21.7%)	65 (26.2%)	0.52
Digoxin	35 (23.6%)	151 (25.7%)	0.60	25 (22.5%)	116 (25.4%)	0.52	17 (25.4%)	66 (19.6%)	0.28	13 (28.3%)	49 (19.8%)	0.19
Nitrate	44 (29.7%)	162 (27.6%)	0.61	31 (27.9%)	114 (25%)	0.53	19 (28.4%)	68 (20.2%)	0.14	10 (21.7%)	42 (16.9%)	0.43
Calcium channel blocker	38 (25.7%)	103 (17.5%)	0.025	31 (27.9%)	91 (20.0%)	0.07	24 (35.8%)	70 (20.8%)	0.008	15 (32.6%)	60 (24.1%)	0.22
Angiotensin receptor blocker	8 (5.4%)	19 (3.2%)	0.21	8 (7.2%)	32 (7.0%)	0.94	5 (7.5%)	31 (9.2%)	0.65	8 (17.4%)	32 (12.9%)	0.42
Amiodarone	40 (27.0%)	203 (34.6%)	0.08	33 (29.7%)	129 (28.3%)	0.76	19 (28.4%)	73 (21.7%)	0.23	10 (21.7%)	49 (19.8%)	0.76
Oral anticoagulant	41 (27.7%)	173 (29.5%)	0.67	32 (28.8%)	157 (34.4%)	0.26	17 (25.4%)	106 (31.5%)	0.32	14 (30.4%)	90 (36.3%)	0.45
Platelet aggregation inhibitor	48 (32.4%)	220 (37.5%)	0.25	36 (32.4%)	156 (34.2%)	0.72	17 (25.4%)	121 (35.8%)	0.10	9 (19.6%)	91 (36.7%)	0.024
Statins	22 (14.9%)	83 (14.1%)	0.81	16 (14.4%)	74 (16.2%)	0.65	16 (23.9%)	82 (24.3%)	0.94	13 (28.3%)	93 (37.7%)	0.22

ACE = angiotensin-converting enzyme.

2-sided log-rank test. The limit of statistical significance was $p \leq 0.05$. Data on survival of the 2 groups were compared with the expected survival of persons of the same age and gender in the Somme department (France). Control data were obtained from French life tables of the Somme department for 1999 provided by the French Institute of Statistics and represent the survival of the Somme general population. Relative survival was computed as the ratio of observed-to-expected survival (observed number of deaths/expected number of deaths in the general population). Data were entered into a SPSS 13.0 statistical software file on a PC (SPSS Inc., Chicago, Illinois) after approval by the CNIL (French computers and privacy commission).

Results

The study population comprised 799 patients (mean age 75 ± 12 years). One hundred fifty-six patients (19.5%) had a history of COPD. Table 1 presents the baseline characteristics of patients with and without COPD. Patients with COPD were predominantly men and more often smokers. Etiologies, prevalence of other noncardiac co-morbidities, and results of complementary investigations were comparable between the 2 groups.

Significant differences were observed between the 2 groups for prescription of HF therapeutic classes (Table 2). Beta blockers were administered less often in patients with COPD at discharge and during the entire follow-up. Only 6.1% of patients with COPD received β -blocker treatment at discharge. During the 5-year follow-up, this proportion did not exceed 10% (Table 2). Higher discharge and 1-year prescription rates of loop diuretics were given to patients with COPD.

During the 5-year follow-up, 107 patients with COPD died (69%). Three- and 5-year survival rates of patients with COPD were 44% and 31%, respectively, compared with 54% and 42%, respectively, in patients without COPD ($p = 0.03$). Compared with the expected survival of the age- and gender-matched general population (Figure 1), the 3- and 5-year survival rates in patients with COPD were dramatically lower (44% vs 82% and 31% vs 71%, respectively). Three- and 5-year relative survival rates (observed/expected survival) of patients with COPD were lower than those of the no-COPD group (53% vs 67% and 44% vs 59%, respectively; Figure 1).

On univariate analysis, a history of COPD was associated with a poorer 5-year outcome (hazard ratio [HR] 1.27, 95% confidence interval [CI] 1.02 to 1.57, $p = 0.032$). A stronger association was observed on multivariable analysis (Figure 2 and Table 3). In patients surviving the index hospitalization, after adjustment for covariates of prognostic importance and treatment on discharge, COPD remained a potent predictor of 5-year outcome (Table 3). COPD was significantly associated with a poorer 5-year outcome in both preserved and reduced EF groups (Table 3). In patients surviving the index hospitalization, on univariate analysis, prescription of a β blocker was associated with better 5-year outcome (HR 0.69, 95% CI 0.54 to 0.88, $p = 0.003$). This relationship was no longer significant on multivariable analysis (HR 0.86, 95% CI 0.65 to 1.14, $p = 0.29$).

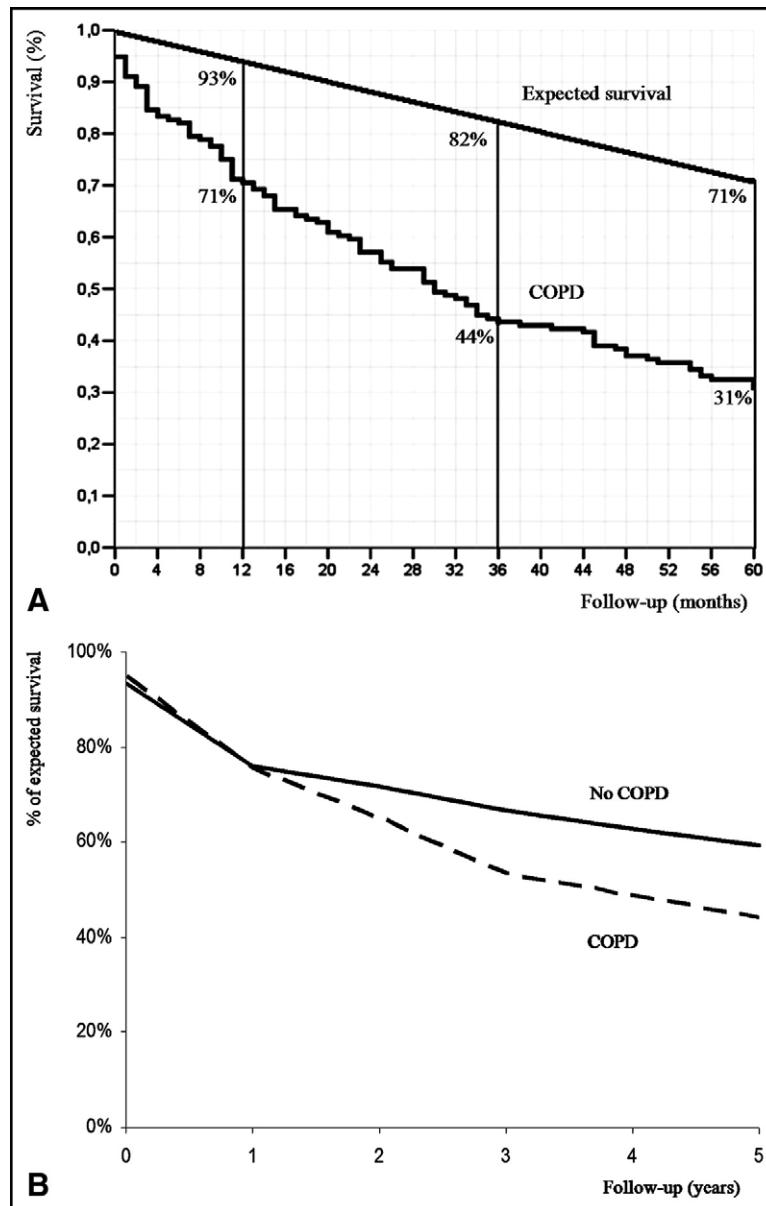


Figure 1. (A) Survival of patients with HF and COPD compared to that of the age- and gender-matched general population. (B) Relative survival of patients with HF and COPD and those with no-COPD expressed as a percentage of expected survival.

Discussion

This is the first study to specifically examine the prognostic impact of COPD in patients with HF. Our population, recruited from all healthcare establishments of the Somme department (France) in 2000, accurately reflects the modern demography of patients with HF. Relative survival curves diverged relatively late, after 1 year of follow-up, suggesting the low impact of COPD on short-term outcome. The long-term prognosis of patients with HF and COPD was poor with 5-year mortality as high as 69%, significantly higher than the 58% mortality observed in patients without COPD. Compared with the survival of the age- and gender-matched general population, the 5-year survival of patients with COPD and HF was dramatically lower. The prognostic impact of COPD was observed in patients with both pre-

served and reduced EF. Very low β -blocker prescription rates were observed in patients with COPD and HF.

HF and COPD are 2 increasingly prevalent conditions associated with premature mortality and poor quality of life. Multiple interactions exist between these conditions. COPD is often responsible for delayed diagnosis of HF, as both conditions have similar symptoms such as dyspnea and poor exercise tolerance. It has been reported that patients with COPD and patients with HF may develop similar skeletal muscle alterations and exercise intolerance.¹⁵

The reported prevalence of COPD among patients with HF ranges between 10% and 33%.^{2,4,7,9} In the EuroHeart Failure survey,¹⁶ 32% of patients were reported to have respiratory disease. In our population, COPD was diagnosed in 19.5% of patients, emphasizing

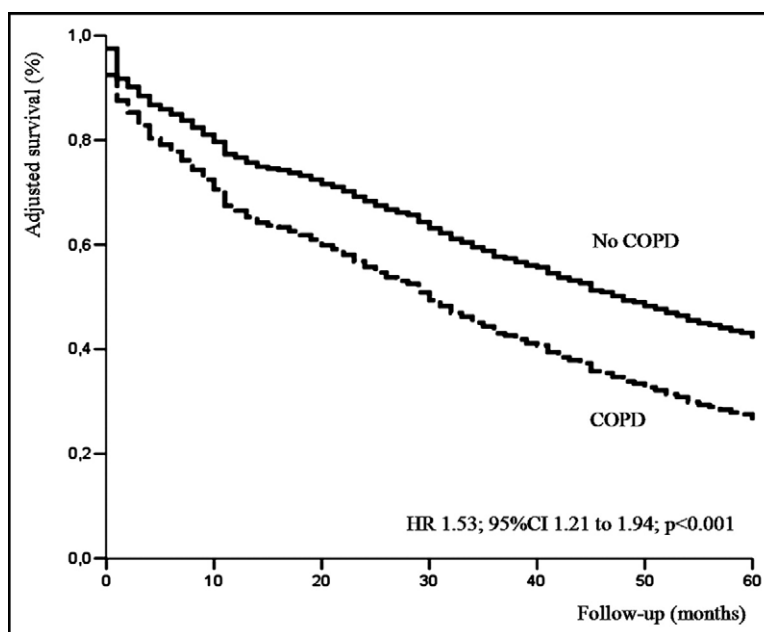


Figure 2. Adjusted 5-year survival curves for patients with HF with and without COPD. This is adjusted to age, gender, smoking, ischemic etiology, hypertensive etiology, diabetes mellitus, stroke, cancer, atrial fibrillation, sodium, creatinine clearance, and hemoglobin.

Table 3

Relative risk of death associated with chronic obstructive pulmonary disease (COPD): results of Cox multivariate analyses

Model	HR	95% CI	p Value
Model 1—Overall population (n = 799)*	1.53	1.21–1.94	<0.001
Model 2—Patients with ejection fraction assessment (n = 662)†	1.65	1.27–2.13	<0.001
Preserved ejection fraction (n = 368)	1.74	1.22–2.49	0.002
Reduced ejection fraction (n = 294)	1.48	1.03–2.14	0.035
Model 3—Survivors to index hospitalization (n = 734)‡	1.70	1.32–2.18	<0.001

* Adjusted to age, gender, smoking, ischemic etiology, hypertensive etiology, diabetes mellitus, stroke, cancer, atrial fibrillation, serum sodium, creatinine clearance, and hemoglobin.

† Adjusted to covariates included in model 1 plus ejection fraction.

‡ Adjusted to covariates included in model 1 plus treatment at discharge (β blockers, ACE inhibitors, loop diuretics, and calcium channel blockers).

ACE = angiotensin-converting enzyme.

the high prevalence of this co-morbidity among patients with HF.

Patients with COPD have an increased risk of developing HF and higher hospitalization and death rates related to HF compared with patients without COPD.^{5,6,17} The prognostic impact of COPD in patients with HF has not been fully elucidated. In a report from the Danish Investigations of Arrhythmia and Mortality of Dofetilide in Congestive Heart Failure database,¹⁰ including a selected population with high prevalence of ischemic heart disease and systolic HF, COPD had an independent negative influence on survival after hospitalization for HF. A few retrospective population-based studies with a relatively short follow-up have identified COPD among other prognostic factors in patients with HF.^{2,8,9} In a large cohort of elderly patients with HF, chronic respiratory disease was the noncardiac co-morbidity associated with the highest adjusted 1-year mortality risk.² In our study, the deleterious effect of COPD on survival was obvious after 1-year of follow-up. Although co-morbid COPD had a relatively limited impact on short-term prog-

nosis, the influence on 5-year outcome was independent of left ventricular function and was considerable.

The coexistence of COPD and HF may be responsible for suboptimal β blockade due to the fear of inducing severe bronchospasm. There is growing evidence that selective β blockade should not be withheld in patients with HF and moderate-to-severe COPD.^{18–20} Recent meta-analyses underscore that selective long-term β blockade does not significantly influence respiratory function in patients with moderate reactive airway disease and chronic obstructive airway disease and must be prescribed more frequently.^{19,20} However, β blockers should be administered with caution in patients with COPD and with significant airway hyper-responsiveness. In “real life” patients with HF and with associated COPD, β -blocker prescription rates remain disappointingly low, as shown in our study, with less than 10% of patients with COPD receiving a β blocker during 5-year follow-up. The beneficial effect of β blockers in patients with HF and COPD needs to be assessed by future interventional studies. Loop diuretics were more frequently pre-

scribed in patients with COPD, suggesting that these patients had more severe HF and more fluid overload.

Our study was exclusively hospital-based, with the advantage of allowing prospective recruitment of all individuals hospitalized for a first episode of HF. Patients with HF treated on an outpatient basis or in long-term care facilities were therefore not included. Our patients were enrolled from all establishments hospitalizing patients with HF: community hospitals, private clinics, and one teaching hospital. This recruitment should reduce referral bias of hospital-based studies performed exclusively in tertiary centers. Diagnostic assessment of HF in the presence of COPD is difficult. The diversity of clinical signs of HF and their lack of specificity can introduce an inclusion bias related to incorrect diagnosis. In our prospective study, the diagnosis of HF was established by the cardiologist or internal physician managing the patient and confirmed by the Framingham criteria,²¹ widely used in epidemiologic surveys. Natriuretic peptides may be helpful in the diagnostic process, but were not systematically used in our study.²² Airflow limitation was not assessed in our cohort during hospitalization. Results of pulmonary function tests were collected from previous medical records when available. Data on the right ventricular function were not available. Our study did not assess sleep apnea, which was reported as a prognostic factor in patients with HF²³ and COPD.

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