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Survival in COPD: Impact of Lung Dysfunction and Comorbidities

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Abstract: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality in industrialized countries. Recent studies investigated the impact of comorbidities on the survival in COPD, but most of them lacked a referent group of comorbidity-matched, nonobstructed individuals.

We examined the 10-year mortality in a sample of 200 COPD patients and 201 nonobstructed controls. They were part of a larger cohort enrolled in a European case–control study aimed at assessing genetic susceptibility to COPD. By design, the COPD group included patients with a forced expiratory volume in 1 second (FEV_1) $\leq$70% predicted. Cases and controls were matched on age, sex, and cumulative smoking history, and shared a nearly identical prevalence of cardiovascular and metabolic disorders. We estimated the hazard of death with Cox regression and percentiles of survival with Laplace regression. COPD was the main exposure variable of interest. Five comorbidities (hypertension, coronary artery disease, prior myocardial infarction, chronic heart failure, and diabetes) were included as covariates in multiple regression models.

The all-cause mortality rate was significantly higher in cases than in controls (43% vs 16%, $P < 0.001$). The unadjusted hazard of death for COPD was 3-fold higher than the referent category ($P < 0.001$), and remained nearly unchanged after introducing the 5 comorbidities in multiple regression. Patients with COPD had significantly shorter survival percentiles than comorbidity-matched controls ($P < 0.001$). Notably, 15% of the nonobstructed controls died by 10.3 years into the study; the same proportion of COPD patients had died some 6 years earlier, at 4.6 years.

In a separate analysis, we split the whole sample into 2 groups based on the lower tertile of FEV_1 and carbon monoxide lung diffusing capacity (DL_{CO}). The hazard of death for COPD patients with low FEV_1 and DL_{CO} was nearly 3.5-fold higher than in all the others ($P < 0.001$), and decreased only slightly after introducing age and chronic heart failure as relevant covariates.

COPD is a strong predictor of reduced survival independently of coexisting cardiovascular and metabolic disorders. Efforts should be made to identify patients at risk and to ensure adherence to prescribed therapeutic regimens.

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Abbreviations: CI = confidence interval, COPD = chronic obstructive pulmonary disease, CT = computed tomography, DL_{CO} = DLCO diffusing capacity of the lung for carbon monoxide, FEV_1 = forced expiratory volume in 1 second, FRC = functional residual capacity, FVC = forced vital capacity, HR = hazard ratio, LAA = low attenuation areas, SVC = slow vital capacity.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently defined as "a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases."[1,2]

In recent years, a number of studies investigated the impact of comorbidities and persistent systemic inflammation on the survival in COPD.[3–8] Most of these studies, however, lacked a referent group of comorbidity-matched, nonobstructed individuals.[4–8] In addition, comorbid conditions were often assessed by questionnaire, or disease codes, and not medically ascertained.[3–7]

The present study was undertaken to assess the relative impact of lung dysfunction and comorbid conditions on long-term survival in COPD. We followed over time a sample of 401 subjects including 200 with an established diagnosis of COPD and 201 nonobstructed controls. All individuals were either current or former smokers. Cases and controls were matched on age, sex, cumulative smoking history, and carefully identified comorbid conditions. COPD status was the main exposure variable of interest, and all-cause mortality the main outcome measure.

METHODS

Ethical Approval

The study was carried out in accordance with the Code of Ethics of the World Medical Association, Helsinki, Finland (Declaration of Helsinki), and was approved by the

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Institutional Review Board (Comitato Etico, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy). Before entering the study, the subjects provided an informed written consent.

Sample

The sample comprised 401 subjects of whom 200 had COPD and 201 were nonobstructed controls. They were evaluated at the Institute of Clinical Physiology, National Research Council, Pisa, Italy, from November 1, 2001 to October 31, 2003 as part of a larger cohort enrolled in a European case–control study aimed at assessing genetic susceptibility to the development of COPD.[9] Potential candidates (N = 559) were evaluated through the help of family physicians in the city of Pisa and surroundings.

The criteria for case recruitment were: firm clinical diagnosis of stable COPD; airflow obstruction as indicated by a postbronchodilator ratio of forced expiratory volume in 1 second (FEV_1) over forced vital capacity (FVC) <0.7, and FEV_1 $\leq 70\%$ of the predicted value; postbronchodilator change in FEV_1 $<12\%$ or <200 mL; and smoking history ≥ 20 pack-years.[9] The patients were excluded if they had an established diagnosis of asthma, chronic lung disorders other than COPD, active lung cancer, history of atopy, or known alpha-1-antitrypsin deficiency.[9] The patients were also excluded if they had a clinically confirmed acute exacerbation in the 4 weeks preceding the study entry.[9]

By design, controls were recruited to match COPD patients on age, gender, and smoking history. The criteria for control recruitment were: FEV_1/FVC ratio >0.7; both FVC and FEV_1 $>80\%$ of predicted value; no family history of COPD; no history of chronic lung disease; and no acute respiratory infection in the 4 weeks preceding the study entry.[9]

Of the 559 subjects screened, 158 (28%) were excluded from the study because of mild airflow obstruction (N = 99); postbronchodilator change in FEV_1 $>12\%$ (N = 7); physiological variant (N = 10); restrictive disorder (N = 14); history of asthma or atopy (N = 7); emphysema without airflow obstruction (N = 2); clinically silent lung cancer (N = 6); sarcoidosis (N = 1); family history of COPD (N = 8); and inability to complete spirometry (N = 4).

Study Protocol

Clinical Assessment

All the subjects were examined by 1 of 3 board-certified chest physicians. Clinical assessment included detailed clinical history and physical examination. Any comorbid condition was recorded (see Appendix for definitions), and so was any medical therapy at the time of enrollment. In searching for comorbidities, pertinent laboratory tests and/or clinical charts of prior hospitalizations were reviewed. If needed, some laboratory tests (eg, echocardiography) were repeated at the time of study entry. COPD patients were then invited to complete a self-administered quality-of-life questionnaire.[10] A 20 mL blood sample (in lithium heparin) was obtained from all the subjects for genomic studies.

Lung Function Studies

Lung function studies included the measurement of slow vital capacity and FVC, and of FEV_1, before and after bronchodilator. At least 3 spirometric measurements were obtained and the highest values were chosen. Functional residual capacity was measured with the nitrogen washout technique and the carbon monoxide lung diffusing capacity (DL_{CO}) with the single-breath method. Spirometry and DL_{CO} measurements were performed by experienced technicians according to American Thoracic Society/European Respiratory Society standards.[11,12]

Lung Imaging

Posteroanterior and lateral digital chest radiographs were obtained on the day of the recruitment. They were taken at a standard 2-m focus-to-detector distance with the subjects upright, holding their breath at full inspiration (Thorax 2000, IMIX, Tampere, Finland). Kilovoltage and tube current were adjusted to the subject's body build. Two chest physicians (MM and SM) evaluated the chest radiographs for the presence of cardiac, pulmonary, or pleural abnormalities.

Computed tomography (CT) of the thorax was obtained in COPD patients within 3 months of study entry. It was performed on a Toshiba Aquilion 64 detector row scanner (Toshiba, Tokyo, Japan) with the patient holding the breath at full inspiration for 10 seconds. Acquisition setting was 120 kVp with milliAmpere-second (mAs) modulated according to the patient's attenuation as assessed before scan acquisition (range, 60–250 mAs). Slice thickness was set at 0.65 mm. No contrast medium was infused. Scans were reconstructed in the axial, sagittal, and coronal planes, and were imaged at a window level of -600 Hounsfield Units (HU) and a width of 1500 HU. Maximum intensity projection technique was used to evaluate vascular disruption and minimum intensity projection was used to highlight focal areas of low attenuation in the lung parenchyma. Images were examined independently by a chest radiologist and a chest physician for the presence of areas of low attenuation and vascular disruption. The 2 raters were blinded to clinical and lung function data. The severity of emphysema was scored on a nonparametric scale from 0 (no emphysema) to 100 using the panel-grading method of Thurlbeck and Müller.[13] Further details are given elsewhere.[14]

Follow-Up

The 401 individuals were followed up until death or December 31, 2012, whichever occurred first. None of them was lost to follow-up. All the nonobstructed controls were interviewed by phone at 6-month intervals. Whenever required, their family physicians were also called. The patients with COPD were evaluated once a year at the outpatient clinic of our Institution. The main outcome measure was all-cause mortality. The cause of death was established by reviewing clinical files, autopsy findings, or death certificates.

Statistical Analysis

Differences between groups at baseline were assessed by Fisher's exact test for the categorical variables and by Mood's median test for the continuous variables. We evaluated time from study entry to death in 2 groups of subjects: COPD patients (N = 200) and nonobstructed controls (N = 201). COPD status was the main exposure variable of interest. Survival in the 2 groups was estimated with the Kaplan–Meier product–limit estimator. We considered the following comorbidities as potentially important predictors of survival: systemic arterial hypertension, coronary artery disease, prior acute myocardial infarction, chronic heart failure, and diabetes. We created a 3-level categorical variable for the total number of comorbidities (0, 1, and 2+). We also evaluated the potential residual confounding by

TABLE 1. Baseline Characteristics of the Study Sample

Characteristic	COPD (N = 200)		No COPD (N = 201)		*P* Value
Age, y	66	(61–70)	65	(61–70)	0.258
Male sex	178	(89)	172	(86)	0.369
BMI, kg/m^2	27	(24–31)	28	(25–30)	0.508
Current smoker	97	(48.5)	101	(50)	0.766
Pack-years of smoking	48	(39–60)	40	(33–50)	<0.001
FEV_1/FVC, %	52	(43–62)	76	(73–78)	<0.001
FEV_1, % predicted	54	(42–65)	95	(88–105)	<0.001
DL_{CO}, % predicted	76	(58–86)	96	(86–108)	<0.001
Chronic phlegm	116	(58)	46	(23)	<0.001
Emphysema*	87	(43.5)	0	(0)	<0.001

BMI = body mass index, DL_{CO} = diffusing capacity of the lung for carbon monoxide, FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.
Data are medians (interquartile range) or numbers (%).
*Assessed on computed tomographic images.

pack-years of smoking. We estimated the 5th, 10th, and 15th percentiles of survival with Laplace regression[15] and hazard ratio (HR) of death with Cox regression. Survival percentiles were used as they offer a comprehensive picture of the covariate effects on survival time while overcoming some interpretational limitations of the HR.[16] The proportionality of the hazard functions in COPD and nonobstructed controls was tested with Schoenfeld's residuals.

In a secondary analysis, we split the whole sample (N = 401) in 4 groups based on the first tertile of the frequency distribution of FEV_1 and DL_{CO} (both expressed as percent predicted). Group 1 (FEV_1 ≤61% and DL_{CO} ≤77%) included 85 subjects, all with COPD; group 2 (FEV_1 ≤61% and DL_{CO} >77%) 51 subjects, all with COPD; group 3 (FEV_1 >61% and DL_{CO} ≤77%) 49 subjects of whom 24 with COPD; and group 4 (FEV_1 >61% and DL_{CO} >77%) 216 subjects of whom 40 with COPD. The survival in each combination of low and high FEV_1 and DL_{CO} was estimated with the Kaplan–Meier estimator. In group 1, cumulative survival was substantially shorter than in any of the remaining groups, which were, in turn, similar. Therefore, in the subsequent analyses, the 3 remaining groups were pooled together. HRs and the 5th, 10th, and 15th percentiles of survival were estimated with Cox regression and Laplace regression, respectively. The proportionality of the hazard functions for group 1 and the 3 other groups pooled together was tested with Schoenfeld's residuals. Stata version 13 (Statacorp, College Station, TX) was utilized for all the analyses.

RESULTS

Sample Characteristics

The baseline characteristics of the study sample are given in Tables 1–3. Matching between cases and

TABLE 2. Comorbid Conditions

Current or Prior Disease	COPD (N = 200)		No COPD (N = 201)		*P* Value
Hypertension	95	(47.5)	75	(37)	0.043
Coronary artery disease	60	(30)	55	(27)	0.582
Prior myocardial infarction	19	(9.5)	13	(6.5)	0.275
Chronic heart failure	27	(13.5)	17	(8.5)	0.112
Left heart valvular disease	8	(4)	5	(2.5)	0.416
Persistent atrial fibrillation	10	(5)	7	(3.5)	0.470
Aortic aneurysm	4	(2)	3	(1.5)	0.724
Prior stroke	2	(1)	3	(1.5)	1.000
Prior PE or DVT	5	(2.5)	3	(1.5)	0.503
Prior cancer	7	(3.5)	10	(5)	0.621
Prior tuberculosis	4	(2)	2	(1)	0.449
Chronic renal failure	2	(1)	1	(0.5)	0.623
Diabetes mellitus	22	(11)	30	(15)	0.298
Dyslipidemia	61	(30.5)	74	(37)	0.205
Thyroid dysfunction	18	(9)	11	(5)	0.183
Chronic hepatitis C	7	(3.5)	9	(4.5)	0.799
Peptic ulcer	8	(4)	10	(5)	0.810

DVT = deep vein thrombosis, PE = pulmonary embolism.
Data are numbers (%).

TABLE 3. Medications

Type of Medication	COPD (N = 200)		No COPD (N = 201)		*P* Value
Inhaled bronchodilators	139	(69.5)	0	(0)	<0.001
Inhaled corticosteroids	128	(64)	0	(0)	<0.001
Oral theophylline	48	(24)	0	(0)	<0.001
Long-term oxygen	14	(7)	0	(0)	0.007
ACE inhibitors	54	(27)	59	(29)	0.657
Calcium channel blockers	45	(22.5)	39	(19)	0.464
Beta-blockers	34	(17)	22	(11)	0.086
Nitrates	31	(15.5)	31	(15)	1.000
Digoxin	22	(11)	7	(3)	0.004
Angiotensin II receptor antagonists	8	(4)	10	(5)	0.810
Antiarrhytmic drugs	11	(5.5)	5	(2.5)	0.135
Diuretics	52	(26)	30	(15)	0.006
Warfarin	15	(7.5)	10	(5)	0.311
Aspirin	48	(24)	54	(27)	0.567
Oral hypoglicemic drugs/insulin	17	(8.5)	21	(10)	0.609
Statins	37	(18.5)	47	(23)	0.269
Thyroid replacement therapy	7	(3.5)	4	(2)	0.380
Antidepressants	4	(2)	4	(2)	1.000

ACE = angiotensin converting enzyme.
Data are numbers (%).

nonobstructed controls was nearly perfect as regards age and sex. Although all the subjects met the minimum requirement of 20 pack-years of smoking, the cumulative smoke exposure was significantly higher in COPD patients than in nonobstructed individuals ($P < 0.001$). Based on the Global Initiative for Chronic Obstructive Lung Disease criteria,[1] the degree of airflow obstruction was moderate ($50\% \leq FEV_1 < 80\%$) in 122 (61%) of 200 COPD patients, severe ($30\% \leq FEV_1 < 50\%$) in 62 (31%), and very severe ($FEV_1 < 30\%$) in 16 (8%).

The prevalence of cardiovascular, metabolic, or endocrine disorders was very similar in the 2 groups (Table 2), and so was the number of coexisting comorbid conditions regarded as potentially relevant predictors of survival (Figure 1).

Survival Analysis

The patients were followed until death (118/401 = 29%) or end of follow-up (283/401 = 71%). They provided 3517 person-years and a median follow-up time of 9.9 years (interquartile range, 8.6–10.7 y). Most deaths (90/118 = 76%) were in-hospital deaths. The causes of death are reported in Figure 2. The all-cause mortality rate was 43% (86/200) among cases and 16% (32/201) among controls ($P < 0.001$).

Kaplan–Meier-estimated cumulative survival was significantly shorter in COPD patients than in nonobstructed controls ($P < 0.001$) (Figure 3). The results of Cox regression are given in Table 4. The unadjusted hazard of death for COPD was 3-fold higher than the referent category (model 1: HR 3.21, 95% confidence interval [CI]

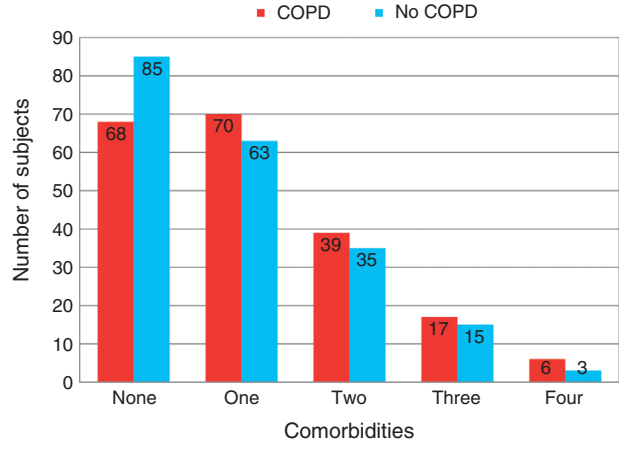

FIGURE 1. Number of coexisting comorbid conditions (hypertension, coronary artery disease, prior myocardial infarction, chronic heart failure, and diabetes mellitus) in 200 COPD patients and 201 nonobstructed controls. Differences between groups are not statistically significant ($P > 0.10$).

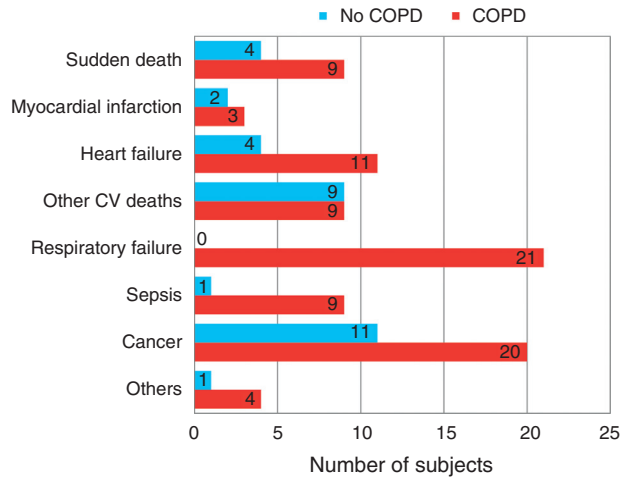

FIGURE 2. Causes of death in 200 COPD patients and 201 nonobstructed controls. Other cardiovascular (CV) deaths are: stroke (N = 8), irreversible cardiac arrhythmia (N = 4), intestinal infarction (N = 3), pulmonary embolism (N = 1), rupture of cardiac aneurysm (N = 1), and death during heart transplantation (N = 1). "Others" include: hemorrhagic shock (N = 3) and multiorgan failure (N = 2). With the exception of respiratory failure, differences between groups are not statistically significant ($P > 0.05$).

2.14–4.82). The presence of any 1 of the 5 comorbid conditions did not significantly increase the hazard of death, but the coexistence of any 2 nearly doubled it (Table 4). The comorbidity-adjusted HR of death for COPD was 2.9 (95% CI 1.91–4.39), but remained highly statistically significant. In Cox model 3, all the 5 comorbidities of interest were included in multiple regression. It appears that the hazard of death varies substantially depending on the type of comorbidity, chronic heart failure being the strongest independent predictor of reduced survival (Table 4). Nevertheless, the hazard of death associated with COPD remained highly statistically significant. By contrast, cumulative smoke exposure had no residual effect on the estimated hazard of death (Table 4).

The results of Laplace regression are graphically displayed in Figure 4. Each stacked block represents 5%, 10%, and 15% of the patients dying in each group. Calculations are based on model 3 in Table 4 when all the other predictors are set equal to their sample median value. The plot shows that the survival was significantly better in nonobstructed controls than in COPD patients ($P < 0.001$). Fifteen percent of the nonobstructed controls died by 10.3 years into the study; the same proportion of patients with COPD had died some 6 years earlier.

In a separate analysis, we split the whole sample in 2 groups based on the lower tertile of FEV_1 and DL_{CO}. Table 5 summarizes the baseline characteristics of the 85 COPD patients in the lower tertile against the others (201 nonobstructed referents and 115 COPD). As expected, the prevalence of structural emphysema in the former group was significantly higher ($P < 0.001$), and so was the cumulative cigarette consumption ($P < 0.005$). The patients in the lower tertile featured a significantly higher prevalence of chronic heart failure and a lower prevalence of diabetes mellitus ($P < 0.05$).

The unadjusted HR of death for patients in the lower tertile of FEV_1 and DL_{CO} was 3.47 (95% CI 2.40–5.02), and decreased slightly after introducing age, pack-years of

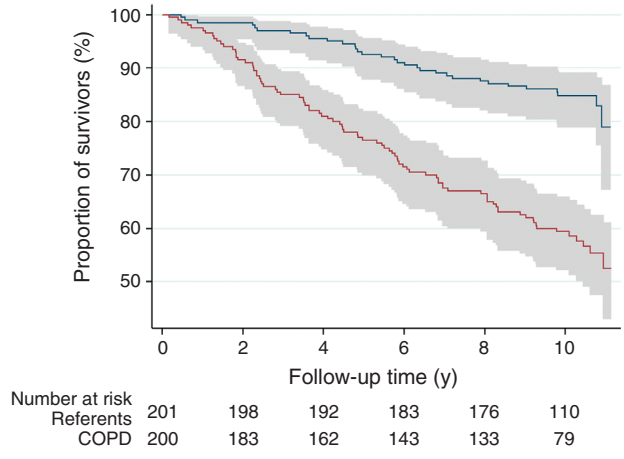

FIGURE 3. Kaplan–Meier survivor curves in 200 COPD patients (red step curve) and 201 nonobstructed controls (blue step curve). Shaded areas indicate 95% confidence intervals. $P < 0.001$ by log-rank test.

TABLE 4. Hazard Ratios of Death With Cox Regression

Variable	Model 1	Model 2	Model 3
COPD	3.21 (2.14–4.82)*	2.90 (1.91–4.39)*	3.07 (2.01–4.69)*
Comorbidity			
1	—	1.06 (0.65–1.71)	—
2	—	1.91 (1.22–3.00)†	—
Pack-years of smoking	—	1.01 (0.99–1.02)	1.00 (0.99–1.01)
Hypertension	—	—	0.89 (0.62–1.29)
Coronary artery disease	—	—	1.81 (1.14–2.85)‡
Prior myocardial infarction	—	—	0.93 (0.50–1.74)
Chronic heart failure	—	—	2.72 (1.67–4.44)*
Diabetes mellitus	—	—	0.64 (0.36–1.13)

COPD = chronic obstructive pulmonary disease.
Values in brackets are 95% confidence intervals.
*$P < 0.001$.
†$P < 0.01$.
‡$P < 0.05$.
Model 1 = no comorbidity.
Model 2 = 1 or 2 comorbidities.
Model 3 = all 5 comorbidities.

smoking, chronic heart failure, and diabetes mellitus as relevant covariates (Table 6). Laplace regression-estimated percentiles of survival are shown in Figure 5. They are calculated by setting age and chronic heart failure equal to the sample median value (66 y and 0, respectively). For each percentile, survival was significantly shorter among patients in the lower tertile of lung function than in all the others ($P < 0.001$).

DISCUSSION

We examined the 10-year mortality in 2 equally sized samples of COPD patients and nonobstructed controls. The 2 groups were matched on age, sex, and cumulative smoking history, and shared a nearly identical prevalence of cardiovascular and metabolic disorders (either single or in combination). The latter finding comes of no surprise because all the individuals recruited for the study were exposed to a common risk factor, that is, heavy cigarette smoking.

Our results can, thus, be summarized as: the all-cause mortality rate is significantly higher in cases than in non-obstructed controls; the unadjusted hazard of death for COPD is 3-fold higher than the referent category, and remains nearly unchanged after introducing 5 relevant comorbidities as covariates in Cox regression; as indicated by Laplace regression, patients with COPD have significantly shorter survival percentiles than comorbidity-matched controls; among the 5 relevant comorbidities introduced in multiple regression, chronic heart failure is the strongest independent predictor of reduced survival; the hazard of death for patients in the lower tertile of FEV_1 and DL_{CO} is nearly 3.5-fold higher than in all the others, and only slightly decreases after introducing age and chronic heart failure as

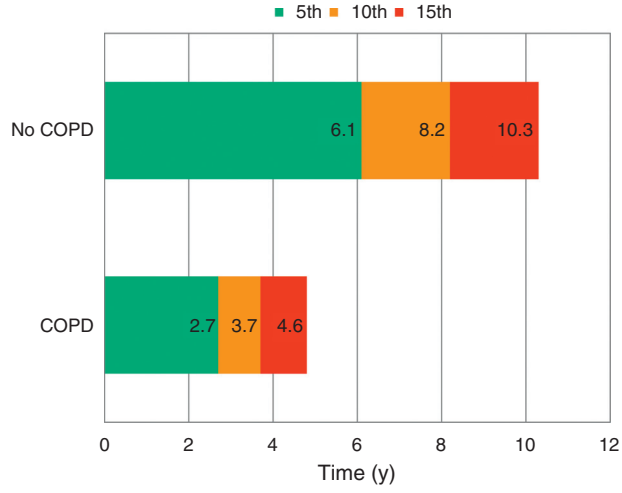

FIGURE 4. Laplace regression estimates of the 5th, 10th, and 15th survival percentiles in COPD patients against nonobstructed controls. For each percentile, survival is significantly shorter in cases than in controls ($P < 0.001$).

TABLE 5. Baseline Characteristics of Patients in Lower Tertile of FEV_1 and DL_{CO} Against All Others

Characteristics	Lower Tertile (N = 85)		All others (N = 316)		*P* Value
Age, y	66	(61–71)	65	(61–70)	0.465
Male sex	72	(85)	278	(88)	0.463
Pack-years of smoking	49.5	(40–59)	43	(35–53)	0.002
Emphysema*	59	(69)	28	(9)	<0.001
FEV_1, % predicted	42	(32–51)	87	(66–99)	<0.001
DL_{CO}, % predicted	57	(47–66)	92	(81–105)	<0.001
Hypertension	34	(40)	136	(43)	0.711
Coronary artery disease	23	(27)	92	(29)	0.786
Prior myocardial infarction	7	(8)	25	(8)	1.000
Chronic heart failure	15	(18)	29	(9)	0.032
Diabetes mellitus	5	(6)	47	(15)	0.029

DL_{CO} = diffusing capacity of the lung for carbon monoxide, FEV_1 = forced expiratory volume in 1 second.
Data are medians (interquartile range), or numbers (%). For abbreviations, see Table 1.
*Assessed on computed tomographic images.

relevant covariates; and similarly, the adjusted survival percentiles in patients with low FEV_1 and DL_{CO} are significantly shorter than in all the other individuals.

Spirometric indices, such as FEV_1 and FVC, are used in clinical practice for the diagnosis, staging, and prognostication of COPD, but they are deemed insufficient for the full characterization of patients with established COPD.[17] Large-scale prospective studies were therefore conducted to define clinically relevant COPD phenotypes, and identify biomarkers, correlated with such phenotypes, that might predict the disease progression and the effect of therapeutic interventions.[4,6–8] Other studies focused on the prognostic impact of comorbid conditions in patients with COPD.[3,5]

Divo et al[5] followed 1659 COPD patients (89% male, mean age 66 y, mean FEV_1 49% predicted) over a median of 4.3 years to assess the impact of comorbid conditions on overall survival. They coined the term "comorbidome" to indicate a constellation of 12 comorbidities that were significant predictors of mortality, and developed a COPD comorbidity index based on the HR of the death associated with each comorbidity. As expected, some forms of cancer (breast, pancreatic, esophageal, and lung) significantly increased the risk of death. Surprisingly enough, "anxiety" turned out to be the strongest predictor of death (HR = 13.76).[5]

The results of the study by Divo et al led some clinical investigators to infer that impairment of lung function in COPD carries little prognostic weight as compared with comorbidities because the former is not reversible whereas some comorbid conditions are amenable to treatment.[18]

It should be considered that: some forms of cancer, such as those alluded to in the study by Divo et al, are associated with poor prognosis independently of the coexistence of COPD; and the likelihood of having 2 or more potentially life-threatening disorders increases as a function of age so that the "comorbidome" concept applies to any clinical disease and not just to COPD. In other words, COPD may happen to be a serious (and often unrecognized) comorbid condition in patients who are first diagnosed as having major cardiovascular disorders.[19,20]

In reality, most of the reported studies[4–8] lacked a referent group of comorbidity-matched, nonobstructed individuals. This precluded the possibility to dissect out the relative contribution of chronic lung dysfunction and comorbidities (or systemic inflammation) on overall survival in COPD.

As shown in Table 5, nearly 70% of the COPD patients in the lower tertile of lung function had evidence of emphysema on CT. That emphysema is an independent predictor of reduced survival is borne out by the results of a recent population-based Norwegian study.[21] In that study, the extent of emphysema was quantified by CT as percent of low attenuation areas (LAAs). Among the individuals with LAA <3%, the 8-year mortality rate was 4%, but it rose to 44% in those with LAA ≥10%. After adjusting for FEV_1, age, COPD status, body mass index, and inflation level, the survival percentiles in individuals with LAA ≥10% were significantly shorter than in the lowest emphysema category taken as referent.[21]

Undoubtedly, CT of the thorax may add valuable information as regards the extent of structural emphysema. We do

TABLE 6. Hazard Ratios of Death for Patients in Lower Tertile of FEV_1 and DL_{CO} Against All Others

Variable	Hazard Ratio	(95% CI)	*P* Value
Lower tertile of FEV_1 and DL_{CO}	3.38	(2.40–5.02)	<0.001
Age	1.11	(1.07–1.15)	<0.001
Pack-years of smoking	1.00	(0.99–1.02)	0.322
Chronic heart failure	2.71	(1.74–4.24)	<0.001
Diabetes mellitus	1.06	(0.61–1.86)	0.837

CI = confidence interval, FEV_1 = forced expiratory volume in one second, DL_{CO} = diffusing capacity of the lung for carbon monoxide.

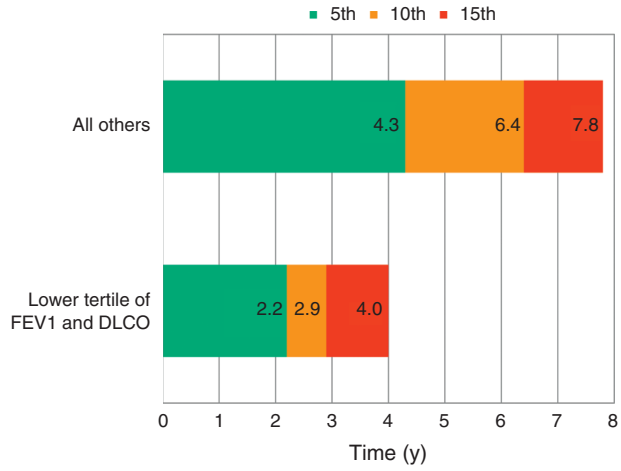

FIGURE 5. Laplace regression estimates of the 5th, 10th, and 15th survival percentiles in the whole study sample split in 2 groups based on the lower tertile of FEV_1 and DL_{CO}. For each percentile, survival is significantly shorter among patients in lower tertile of FEV_1 and DL_{CO} than in all the others ($P < 0.001$). DL_{CO} = lung diffusing capacity for carbon monoxide, FEV_1 = forced expiratory volume in 1 second.

believe, however, that simple spirometry and measurement of lung diffusing capacity are sufficient to assess the degree of lung function impairment in routine clinical practice. As such, they can be used as reliable predictors of survival in COPD.[22,23]

As indicated in Table 4, the coexistence of cardiovascular comorbidities (particularly, chronic heart failure) amplifies the hazard of death in patients with COPD. Yet, this should not make clinicians overlook the negative impact that lung dysfunction, especially if severe, may have on long-term survival in COPD.

Thus, every effort should be made to carefully assess the degree of airflow obstruction and the impairment of lung diffusing capacity. This issue is fundamental in view of the growing evidence that patients with COPD often fail to adhere to the treatments including inhalation therapy, supplemental oxygen, or pulmonary rehabilitation programs.[24] Nonadherence, in turn, contributes to rising rates of hospitalization, death, and health care costs.[25]

The importance of assessing lung function also applies to patients who are first diagnosed as having major chronic cardiovascular disorders, especially if they are current or former heavy smokers. In connection to this, it has been recently reported that FEV_1 and alveolar volume <80% of predicted value are both strong independent predictors of death in patients with systolic heart failure.[26,27]

Study Limitations

First, the sample size is relatively small and originates from a single referral center. Second, the individuals recruited into the study are all white Caucasians, so our findings may not apply to other ethnic groups. Third, only a minority of the subjects (13%) are females. Thus, further studies are needed to assess the gender-specific impact of lung dysfunction and comorbid conditions on overall survival in COPD.

CONCLUSIONS

In sum, our study indicates that COPD is a strong predictor of reduced survival independently of coexisting cardiovascular and metabolic disorders. Efforts should then be made to identify patients at risk by simple lung function tests and to ensure adherence to prescribed therapeutic regimens.

Appendix

Definitions of Comorbid Conditions

Systemic arterial hypertension was considered to be present if there was documented persistent elevation of arterial pressure (systolic >150 mmHg or diastolic >90 mmHg) or if the patient was receiving antihypertensive medication. Coronary artery disease was considered to be present if 1 of the following criteria were met: typical angina on exertion, use of antianginal medication, and any prior myocardial infarction documented by electrocardiogram and cardiac enzyme elevation. Left heart valvular disease was recorded if there was hemodynamic or echocardiographic evidence of mitral or aortic stenosis or incompetence. Chronic heart failure was recorded if, on transthoracic echocardiography, the left ventricular ejection fraction was ≤40% in at least 2 consecutive studies obtained in the year preceding the study entry. Cerebrovascular disorders included transitory ischemic attacks and stroke, and were recorded if documented any time prior to the enrollment in the study. Pulmonary embolism was recorded if there had been episodes of embolism, diagnosed by computed tomographic angiography or lung scintigraphy, that required anticoagulant therapy. Similarly, deep vein thrombosis was recorded if there had been episodes of venous thrombosis, documented by compression ultrasonography of the lower or upper extremities, requiring anticoagulant therapy. Diabetes mellitus was considered to be present if the patient was on long-term therapy with insulin or oral hypoglycemic drugs. Hypercholesterolemia was recorded if the blood cholesterol was >200 mg/dL and the high-density lipoprotein cholesterol was <40 mg/dL, or if the patient was on long-term statin therapy. Hypertriglyceridemia was recorded if triglyceride levels were >150 mg/dL. Hypercholesterolemia and hypertriglyceridemia were grouped under the term "dyslipidemia." Documented hyperthyroidism or hypothyroidism of any cause requiring appropriate medical treatment was recorded as "thyroid dysfunction." Chronic hepatitis C was recorded if there were elevated serum aminotransferases for longer than

6 months, anti-hepatitis C virus (HCV) antibodies present in serum, and positive testing for HCV RNA by polymerase chain reaction. Chronic renal failure was recorded if the estimated glomerular filtration rate was <60 mL/min on repeated measurements prior to enrollment in the study.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management and Prevention of COPD*. 2011. http://www.goldcopd.org. Accessed May 19, 2012.
2. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet*. 2007;370:765–773.
3. Mannino DM, Thorn D, Swensen A, et al. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J*. 2008;32:962–969.
4. Agustí A, Edwards LD, Rennard SI, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS ONE*. 2012;7:e37483.
5. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186:155–161.
6. Lange P, Marott JL, Vestbo J, et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification. A study of the general population. *Am J Respir Crit Care Med*. 2012;186:975–981.
7. Thomsen M, Dahl M, Lange P, et al. Inflammatory biomarkers and comorbidities in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2012;186:982–988.
8. Vanfleteren LEGW, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187:728–735.
9. Chappell S, Daly L, Morgan K, et al. Cryptic haplotypes of SERPIN A1 confer susceptibility to chronic obstructive pulmonary disease. *Hum Mutat*. 2006;27:103–109.
10. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of heath status for chronic airflow limitation. The St. George's respiratory questionnaire. *Am Rev Respir Dis*. 1992;145:1321–1327.
11. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319–338.
12. MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26:720–735.
13. Thurlbeck WM, Müller Emphysema: NL. Emphysema: definition, imaging, and quantification. *Am J Roentgenol*. 1994;163:1017–1025.
14. Miniati M, Monti S, Basta G, et al. Soluble receptor for advanced glycation end products in COPD: relationship with emphysema and chronic cor pulmonale: a case-control study. *Respir Res*. 2011;12:37.
15. Bottai M, Zhang J. Laplace regression with censored data. *Biometrical J*. 2010;52:487–503.
16. Hernán MA. The hazard of hazard ratios. *Epidemiology*. 2010;21:13–15.
17. Vestbo J, Anderson W, Coxson HO, et al.; ECLIPSE Investigators. Evaluation of COPD longitudinally to identify predictive surrogate end-points (ECLIPSE). *Eur Respir J*. 2008;31:869–873.
18. Fabbri LM, Beghè B, Agustí A. COPD and the solar system. Introducing the chronic obstructive pulmonary disease comorbidome. *Am J Respir Crit Care Med*. 2012;186:117–119.
19. Iversen KK, Kjaergaard J, Akkan D, et al. ECHOS Lung Function Study Group. Chronic obstructive pulmonary disease in patients admitted with heart failure. *J Intern Med*. 2008;264:361–369.
20. Iversen KK, Kjaergaard J, Akkan D, et al. ECHOS Lung Function Study Group. The prognostic importance of lung function in patients admitted with heart failure. *Eur J Heart Fail*. 2010;2:685–691.
21. Johannessen A, Skorge TD, Bottai M, et al. Mortality by level of emphysema and airway wall thickness. *Am J Respir Crit Care Med*. 2013;187:602–608.
22. Boutou AK, Shrikrishna D, Tanner RJ, et al. Lung function indices for predicting mortality in COPD. *Eur Respir J*. 2013;42:616–625.
23. Cerveri I, Rossi A, Brusasco V. Look at comorbidities, but don't forget lung function. *Am J Respir Crit Care Med*. 2013;187: 328–329.
24. Bender BG. Nonadherence in chronic obstructive pulmonary disease patients: what do we know and what should be done next. *Curr Opin Pulm Med*. 2014;20:132–137.
25. Vestbo J, Anderson J, Calverley P, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. *Thorax*. 2009;64:939–943.
26. Miniati M, Monti S, Bottai M, et al. Forced expiratory volume in one second: prognostic value in systolic heart failure. *Int J Cardiol*. 2013;168:1573–1574.
27. Miniati M, Monti S, Bottai M, et al. Prognostic value of alveolar volume in systolic heart failure: a prospective observational study. *BMC Pulm Med*. 2013;13:69.