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Comorbidities and Risk of Mortality in Patients with COPD

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At a Glance

Scientific Knowledge of the Subject:

Patients with COPD frequently suffer from concurrent comorbidities, yet their nature, prevalence and impact on mortality is poorly understood.

What This Study Adds to the Field:

A systematic evaluation of the spectrum and prevalence of comorbidities affecting patients with wide range of COPD severity attending pulmonary clinics. Establish the relationship between these comorbidities and the risk of death over a median of 51 months. Express the prevalence and mortality risk using an orbital bubble chart (the "Comorbidome") and a quantitative risk stratification comorbidity tool (The COTE Index) that is simpler than the Charlson Score.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

Abstract

Rationale

Patients with COPD are afflicted by comorbidities. Few studies have prospectively evaluated COPD comorbidities and mortality risk.

Methods

We followed 1664 patients with COPD in five centers for a median of 51 months. Systematically, 79 comorbidities were recorded. We calculated mortality risk using Cox proportional hazard, and developed a graphic representation of the prevalence and strength of association to mortality in the form of a "comorbidome". A COPD comorbidity index (COTE) was constructed based on the comorbidities that increase mortality risk using a multivariate analysis. We tested the COTE index as predictors of mortality and explored whether the COTE added predictive information when used with the validated BODE index.

Results

Fifteen of 79 comorbidities differed in prevalence between survivors and non-survivors. Of those, 12 predicted mortality and were integrated into the COTE index. Increases in the COTE index were associated with an increased risk of death from both COPD (HR 1.13, 95% CI 1.08-1.18, P<0.001) and non-COPD related causes (HR 1.18, 95% CI 1.15-1.21, P<0.001). Further, increases in the BODE and COTE were independently associated with increased risk of death. A COTE of ≥4 points increased by 2.2-fold the risk of death (HR 2.26-2.68, p values <0.001) in all BODE quartile.

Conclusion

Comorbidities are frequent in COPD and 12 of them negatively influence survival. A simple

disease specific comorbidities index (COTE) helps assess mortality risk in patients with COPD.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is an important cause of morbidity and mortality around the world(1, 2). Patients with COPD frequently suffer from concurrent comorbidities such as such as cardiovascular(3) and cerebrovascular disease(4), lung cancer(5) and diabetes.(6) Those comorbidities were adjudicated as the primary causes of death in over 60% of non-survivors in two large randomized controlled pharmacological trials(7, 8) however, limited data exists on the prognostic value of capturing the effects of these comorbidities in patients with COPD.

Determining the risk of death in COPD has been better ascertained using multidimensional indices like the BODE (Body Mass Index; FEV_1; Dyspnea and Exercise capacity)(9) , the ADO (Age, Dyspnea, FEV_1)(10) and the DOSE indexes (Dyspnea, FEV_1, Smoking status, and Exacerbation frequency)(11) rather than using the classic unidimensional information provided by the FEV_1. However those indices do not systematically include the presence or impact of coexisting diseases. The few studies that have explored COPD related comorbidities (12-16), suggest that compared to age matched controls some comorbidities are more likely to co-exist with COPD(16), that they impact on relevant outcomes such as health related quality of life(12, 13), utilization of health care resources(15), response to intervention(12) and mortality(14, 15). However, these studies were not planned to systematically evaluate the prevalence and role of comorbity in COPD, several were performed in single centers with small number of patients(12, 14), used retrospective administrative database(6, 17, 18), or enrolled patient admitted in the

acute care hospital after and acute exacerbation(14, 15) limiting the applicability of their findings.

Since the inception of the BODE cohort, an ongoing prospective observational multi-national study of COPD outpatients attending pulmonary clinics, we have systematically recorded the presence or subsequent development of comorbidities. We hypothesized that we could determine the prevalence of individual comorbidities and the strength of the association between the number and nature of the comorbidity and risk of death over time. With this information, we developed a point scale index, the COPD specific CO-morbidity TEst (COTE). Finally, we explored whether the COTE index provided additional prognostic information to that provided by the BODE index.

Some of the results of this study have been previously presented in the form of an abstract during the 2011 European Respiratory Society meeting(20).

Materials and methods

Study design and population

The BODE cohort is an ongoing prospective, multicenter, observational study of COPD subjects, recruited from pulmonary clinics in the United States and Spain, with repeated examinations at least every year. The ethics committee at each of the participating centers approved the study and all patients signed informed consent prior to enrollment.

Between November 1997 to March 2009, a total of 1664 subject from all 5 sites were enrolled in the study and followed until either the time of death or to March 2010. The consort diagram for the cohort is shown in Figure E1 (Online data supplement).

The details of the BODE cohort inclusion and exclusion criteria have been previously described(9). In brief, COPD was defined on the basis of a history of smoking (> 10 pack/years) and on lung function test results following the ATS/ERS standards(21). All patients were in clinically stable condition and receiving standard therapy. Subject were excluded if they had primary asthma, inability to take the lung-function and six-minute–walk tests or any condition that could unacceptably increase the subject's risk of performing any of the testing.

Measurements

We recorded age, gender, post-bronchodilator spirometry, the BODE index(9) at baseline and after each visit.

Comorbidities

Comorbidities were systematically recorded through direct questioning for the following conditions: 1. Those diseases included in the Charlson Comorbidity Index(19) (19

comorbidities), 2. All comorbidities listed in the subject's medical record, or 3. Those expressed during enrollment interview and subsequent visits. The diagnosis of a comorbidity was confirmed by either reviewing the patient's medication list, or when feasible by confirmatory test(s) available from their medical records. Conditions that had completely resolved were excluded (i.e. pneumonia).

Survival.

The follow-up time for each subject was determined from the date of enrollment to the date of the last visit or attempt to verify subject status. Death or lost in follow-up was verified by calling each subject or their family if they failed to return for appointments, and if we were unable to reach them, by checking the social security death index (United States). Cause specific mortality was ascertained by each site investigator to the highest detail possible and then categorized in an systematic and blinded fashion by four of the investigators (BC, CC, JZ and MD) as either death related to a) COPD, b) non-COPD respiratory cause, c) cardiovascular, d) cancer, e) other causes, or f) unknown, as previously described(8).

Development of the "Comorbidome" and COTE (COPD Comorbidity Test) index.

To evaluate the strength of the association of the comorbidities with the risk of death, we performed multivariate analyses using Cox proportional –hazards regression including all 79 recorded comorbidities . We integrated this information with the prevalence of the disease to construct the "*Comorbidome*" which is the graphical expression of the comorbidity prevalence and risk of death in the form of an orbital bubble chart.

The COTE index was constructed by scoring those same comorbidities that were associated with a stastically significant hazard of death. The sum of the points intends to capture the individual

or combination of diseases affecting each patient.

Statistical analysis

When appropriate, data for continuous variables are presented as means ± SD or median and 25-75 interquartile range. Group comparison was conducted using Fisher's exact test (for categorical variables) and two-tailed t-tests or the Wilcoxon rank-sum test (for continuous variables). Prevalence is expressed as percentage of the population at risk.

To calculate the effect of the COTE and BODE indexes on the risk of death we fitted stratified Cox models to account for violations of the proportional hazards assumption. Stratified Cox models were fit with a stratification term indicating follow-up times of < 18 months and ≥ 18 months. To assess the predictive value of the COTE index alone and in comparison to the BODE index we used C statistics and the Net Reclassification Index ((22)). The probability of death at 5 years was grouped similarly to those described previously (0 to $< 5\%$, 5% to $< 10\%$, 10% to $< 20\%$ and $\geq 20\%$)(22). A p value of less than 0.05 was considered statistically significance. All analyses were performed using SAS software, version 9.2 (SAS Institute). The study data was collected and managed using REDCap (Research Electronic Data Capture) a secure, web-based data capture application hosted at the Brigham and Women's Hospital-Partners Healthcare System(23).

Results

Characteristics of the cohort

The demographic and baseline characteristics of the 1659 patients included in the analysis are summarized in Table 1. The cohort consisted primarily of Caucasian males with a mean FEV_1 % predicted of 47% with a wide range of airflow obstruction (GOLD stages). The mean BODE index was 3.7 and all BODE quartiles were represented (9) (Table 1). The median follow-up for this cohort was 51 months, interquartile range (IQR) of 28 to 78 months. During the observation period, 40% of the subjects died, and the median follow up for non-survivors was 36 months (IQR 17-55) compared to 62 months (IQR 40-91) for survivors ($p<0.001$) (Figure E1 online supplement). Of the 671 subjects who died during the observation period the primary cause of death could be determined in 551 subjects (82%). Respiratory cause of death was the primary etiology in 328 subject (49%), with COPD representing 268 cases (40%). In 283 patients (42%), death was due to non-respiratory causes; 144 subjects died from cancer (21%) and 51 died from cardiovascular diseases (8%) (Figure E2 online supplement).

Comorbidities

A total of 79 comorbidities were observed in this cohort including some that are gender predominant (breast cancer, benign prostate hypertrophy, prostate cancer, hypogonadism). The average number of comorbidities (+/- SD) was 6.0 +/- 3.5 per subject for the whole cohort, 4.6 +/-3.2 for females, 6.2 +/- 3.5 for males ($p<0.001$). The average number of comorbidities was higher for the non-survivors compared to survivors (6.5 +/- 3.8 and 5.8 +/- 3.3 respectively, $p< 0.001$).

The distribution of the most prevalent (>5%) and significant comorbidities are shown in Figure

1, and expanded to include all of them in Figure E3 and Table E1 of the online supplement. There is a heavy tailed distribution, ranging from 52% to less than 1%. Fifteen comorbidities had a significantly higher prevalence in non-survivors compared with survivors (shown by the presence of asterisks in Figure 1). Using multivariate analysis, only 12 of them increased the risk of death over the study time and were selected to construct the COTE index (Table 2 and Table E2 online supplement).

The COPD Comorbidome

The prevalence of the 12 comorbidities associated with increased risk of death, those with an overall prevalence higher than 10% and the strength of their association with mortality are presented in Figure 2 as an orbital bubble chart. Mortality is fixed at the center, and each comorbidity is represented as a bubble or "planet" with their diameter proportional to the prevalence. Each planet is positioned in a radial "orbit" with the distance to the center scaled from the inverse of the Hazard Ratio (1/hazard ratio). The closer the comorbidity is to the center, the higher the conferred risk. All bubbles associated with a statistically significant increase in mortality are fully inside the doted orbit (1/hazard ratio<1).

COTE Index

The comorbidities included in the COTE index are shown in Table E2 (online supplement). Similar to the Charlson Index(24), a scale value points in the range of 1 to 6 points was assigned to each selected comorbidity in proportion to its hazard ratio (1-1.5 = 1, >1.5-2 = 2 and >2=6 points with the exception other cancers which were assigned 2 points).

The effect of the COTE index on the risk of death varied over time. There was minimal evidence

that an increased COTE index was associated with an increase in the hazard of death in COPD patients followed for < 18 months (hazard ratio [HR] 1.04, 95% Confidence Interval [CI] 0.98-1.10, P=0.18) in contrast an increased COTE index was associated with death in COPD patients followed for ≥ 18 months (HR 1.16, 95% CI 1.13-1.19, P=<0.001). Therefore, the remaining models were fit with a stratification term accounting for this time difference. Overall, the hazard ratio for death conferred by an increase of one point in the COTE index was 1.14 (95% [CI] 1.10-1.16, P=<0.001). Increases in the COTE index were associated with an increased risk of death from both COPD (HR 1.13, 95% CI 1.08-1.18, P<0.001) and non-COPD related causes (HR 1.18, 95% CI 1.15-1.21, P<0.001). The same association was observed at each of the study sites and between Spain and the United States. Using c statistics, the performance of COTE to predict mortality (c value of 0·66, p<0·0001) was similar to that of the CCI (c value of 0·65, p<0·0001).

COTE, BODE and Mortality

In models adjusting for age, gender, race, and the BODE index, an increased COTE index remained a significant predictor of death (HR 1.10, 95% CI 1.08-1.13, P <0.001). To identify the level of the COTE index with the greatest predictive value for death in patients with COPD we used receiver operating characteristic (ROC) curves. A COTE index ≥ 4 resulted in the greatest area under the curve (c=0.63) and was associated with a 2.3-fold increased risk of death (HR 2.3, 95% CI 2.00-2.75, P=<0.001). Comparable to previous studies(9) the BODE index was a significant predictor of death in patients with COPD (c=0.74) however, there was evidence that COTE index added to the predictive value of the BODE index (c=0.79 for the COTE and BODE index, P<0.001 for the addition of the COTE index). Similarly, the COTE index improved the net reclassification of subjects with COPD when added to the BODE index (net reclassification

improvement 23%, SE 3%, P<0.001).

In each BODE quartile those patients with a COTE index of 4 or above had over a 2.2-fold increase in their risk of death (HR 2.26-2.68, p values <0.001 for all groups). This is shown in figure 3 in the form of Kaplan-Meier survival curves stratified by each BODE quartile.

Discussion

This longitudinal observational multicentric study of COPD patients attending pulmonary clinics, in which comorbidities were systematically identified, had three main findings. First, although a large number of comorbidities may be present in patients with COPD, a limited number of easily identifiable ones are independently associated with COPD and non-COPD mortality. Secondly, from the resulting hazard ratio for death and prevalence data of the more frequent comorbidities, a new expression of the relationship of comorbidities and COPD is presented, the COPD "Comorbidome". Thirdly, a new comorbidity risk index (COTE) was developed. This simple index, which provides complementary information to the BODE can help predict which patients with COPD are at increased risk of death regardless of their baseline physiological state.

COPD is a complex respiratory disease that is frequently associated with systemic manifestations(25, 26). Indeed, a low BMI, higher dyspnea scores, and impaired exercise capacity confer a poor prognosis that is independent of the degree of airflow limitation(9). In addition, there is accumulating evidence that patients with COPD are prone to develop other important diseases such as coronary artery disease(6), lung cancer(5), osteoporosis(27),

anemia(28), depression(29) and dysfunctional skeletal myopathy(30). Because the association with these other diseases appears to be stronger in patients with COPD than in patients without the disease(16), Fabbri et al(31) proposed that perhaps COPD was just one more manifestation of a systemic inflammatory syndrome. This concept has received great attention, however, the associations have been explored in databases not specifically designed to evaluate comorbidities or reported in studies where only a selected number of comorbidities were evaluated.

The BODE cohort was recruited with the goal of methodically and longitudinally phenotype COPD patients as seen in pulmonary clinics. As part of that characterization, patients were systematically evaluated for the presence of comorbidities at baseline and at each subsequent visit. Besides the diseases included in the Charlson score that was used to quantify baseline comorbidity, patients were asked to state the development of any new disease or any new form of treatment provided for any ailment during the duration of follow-up. As seen in figure 1 and Figure E2 and Table E1 of the online supplement, a total of 79 different comorbidities were identified over the median follow up time of 51 months. As expected not all of the comorbidities were equally prevalent, with some such as hypertension and hyperlipidemia affecting up to 50% of the patients whereas other had a very low prevalence. Healthcare providers are faced by limitations in the time allotted to evaluate their patients, and therefore, guidance that helps them select comorbidities likely to increase the risk of poor outcome, could help optimize clinical interventions. The results here presented show that of the 79 comorbidities identified, 15 differed significantly between survivors and non-survivors. Of these, 12 were independently associated with increased risk of death (Table 2) and may constitute the core of comorbidities that health care providers should pay increased attention in guiding a targeted personalized screening and treatment or expanding the differential diagnosis in patients with a primary

diagnosis of COPD(32). Some like coronary artery disease and lung cancer are in agreement with previously reported literature(5, 33, 34). However, the increased risk provided by other cancers such as esophageal and pancreatic are less well known and breast cancer and anxiety in women somewhat surprising. Further, the increased risk of death conferred by the presence of interstitial pulmonary fibrosis, peptic ulcer disease, liver cirrhosis and atrial fibrillation/flutter have not been described. These findings raise the possibility of a close interaction amongst these diseases that may share common biological pathways.

One novel finding of this study is the spatial expression of the prevalence of comorbidities and their strength of association with mortality in patients with COPD. This new expression shown in figure 2 that we have termed "COPD-comorbidome" visually conveys the prevalence of the disease (size of the circles) and the risk of death (proximity to the center). Although hypertension, hyperlipidemia and obstructive sleep apnea are highly prevalent, the direct risk for death that these diseases confer is not significant. We believe the most likely reason is that they are all treatable or that they are risk factors for the development of more lethal disease, as is coronary artery disease. On the other hand, selected cancers conferred a great risk for death. Of these, lung cancer stands in a group by itself since it showed an aggregated prevalence of 9%, confirming the strong association between COPD and lung cancer(35). A novel finding in this study was the relative high prevalence of IPF (6%) and its independent strong association with risk of death. This observation provides support to the argument recently proposed by Washko and associates(36) that the combination of interstitial lung abnormalities and COPD, which they found in 8% of the COPD gene cohort, may bear an association mediated by the common risk factor of smoking. Liver cirrhosis and anxiety were also associated with increased risk for death and suggest some correlation with lifestyle and social behavior of this population that should be

easily accessible with medical interview. The identification of anxiety as a risk factor for death particularly in women is intriguing from the perspective of its biological relationship to COPD. However our findings are consistent with previous studies, where anxiety is more prevalent in females(37) and impacts on important patient related outcomes as is the case of rate of exacerbations and hospitalizations(38, 39) . The nature of the association between anxiety, COPD and risk of death should be explored in other cohorts as this condition is potentially treatable(40). The risk conferred by peptic ulcer disease is very interesting in light of the findings reported by the ECLIPSE (41) investigators where one of the predictors of frequent COPD exacerbations was the presence of gastro-esophageal reflux.

To fill the need for a simple specific tool of use to clinicians and researchers to quantify the comorbidities of COPD patients, we developed the COTE index. Our data demonstrate that measurements of comorbidities as captured by the COTE index improve the prognostic accuracy for mortality in COPD when added to the BODE index. Using c statistic,the behavior of the COTE index to predict mortality was similar to that of the Charlson index but it is simpler to construct. The COTE index captures diseases like atrial fibrillation, pulmonary fibrosis or anxiety which confer increased risk of death otherwise not included in the Charlson Index . On the other hand , the Charlson Index includes comorbidities like renal and liver disease, categorized by a severity grading system that is not well defined and, it places very high values to diseases that are currently better-controlled, such as AIDS(24).

To validate the usefulness of the COTE index, we split the cohort into those patients recruited in Spain and those in the United States. The same association was documented at each of the study sites. For Spain the hazard ratio [HR] was 1.12, 95% confidence interval [CI] 1.10-1.15, P=<0.001 whereas in the United States the HR was 1.13, 95% confidence interval [CI] 1.11-

1.16, P=<0.001. The results of this study also show that a combination of BODE and COTE index provide health care workers and researchers with simple tools to better stratify patients and provide a platform for comparative effectiveness research(32).

This study has some limitations. First, there were few women included in the cohort. This was not by design, but it is the reality of the patients attending the clinics where the study is being conducted. However, there were 186 of them and with this number it was possible to identify breast cancer and anxiety as two of the 12 diseases that carried an independent increased risk of death. We find this relationship extremely interesting and worth studying in other cohorts. Secondly, at baseline some patients were excluded because of comorbidities that could cause early death and difficulty in performing all of the tests. Specifically, patients with a recent myocardial infarction (4 months), severe congestive heart failure and untreated cancer were not recruited into the study. However, this should have worked against our findings by decreasing potential contributors to the diseases that have a high prevalence but that also conferred a poor prognosis to patients who developed them during the follow up period, and provide a possible explanation of the better performance of the COTE index after 18 months of observation. In spite of this exclusion at baseline, all three diseases when developed, significantly increased the chance of death over the study time. Thirdly, findings may not apply to all COPD patients, since the patients were recruited from specialty clinics. However, as seen in table 1, there were large number of patients at all GOLD stages and BODE quartiles, and in addition, it is likely that patients such as the ones here studied represent the majority of those seen by practicing physicians in primary care(42).

In summary, we have confirmed that patients with COPD are frequently afflicted by comorbidities. A group of 12 easily identifiable ones confer an independent risk of death and

could form the core of diseases that could be screened by health care providers caring for these patients since for some of them, there are effective interventions that may help decrease the risk of death. We present the “comorbidome” as a novel expression of the prevalence of comorbidity and the strength of their association with risk of death in patients with COPD. Finally, the COTE index developed in this COPD cohort is a simple predictor of risk of death that complement the accepted BODE index and could be used to quantify the burden of comorbidity in the clinical and also in the research setting.

Conflict of interest statement

The authors of this manuscript do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript

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We dedicate this manuscript to honor the legacy of our dear co-author and friend Claudia Cote, MD (1960- 2010) for her outstanding contribution in COPD research and her unconditional friendship. It is only appropriate that the proposed index, if accepted by the pulmonary community, may perpetuate her name in the field to which she devoted her life.

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Figure 1. Comorbidities with >5% prevalence in survivors (green bars) and non-survivors (red bars). The figure also includes those comorbidities with a significantly (identified with an asterisk) higher prevalence in non-survivors compared to survivors regardless of their absolute prevalence (see Figure E2 and Table E1 online supplement for details).

Abbreviations:

AAA= Abdominal Aortic Aneurism, BOOP= Bronchiolitis Obliterans with Organizing Pneumonia or cryptogenic obstructive pneumonitis, BPH= Benign Prostatic Hypertrophy, CAD = Coronary Artery Disease, CHF=Congestive Heart Failure, CRF=Chronic Renal Failure, CVA=Cerebro-Vascular Accident, DJD= Degenerative joint Disease, DVT= Deep Venous Thrombosis, GERD=Gastro-Esophageal Reflux Disease, MAI=Mycobacterium Avium Infection, OSA= Obstructive Sleep Apnea, PAD: peripheral artery disease, Pulmonary HTN+RHF= Pulmonary Hypertension and Right Heart Failure

Figure 2. The "Comorbidome" is a graphical expression of comorbidities with >10% prevalence in the whole cohort, and those comorbidities with the strongest association with mortality (Hazard Ratio > 1, 95% CI >1 and p≤ 0·05). The area of the circle relates to the prevalence of the disease. The proximity to the center (mortality) expresses the strength of the association between the disease and risk of death. This was scaled from the inverse of the Hazard Ratio (1/hazard ratio). All bubbles associated with a statistically significant increase in mortality are fully inside the doted orbit (1/hazard ratio<1). Bubble color represent organ systems or disease clusters (cardiovascular= red, female specific comorbidities= pink , pulmonary=blue, brown=cancer and green=other)

Abbreviations:

A. Fibrillation= Atrial Fibrillation/Flutter, BPH= Benign Prostatic Hypertrophy, CAD = Coronary Artery Disease, CHF=Congestive Heart Failure, CRF=Chronic Renal Failure, CVA=Cerebro-Vascular Accident, DJD= Degenerative joint Disease, GERD=Gastro-Esophageal Reflux Disease, OSA= Obstructive Sleep Apnea, PAD: peripheral artery disease, Pulmonary HTN+RHF= Pulmonary Hypertension and Right Heart Failure

Figure 3. Kaplan-Meier survival curve representing survival probability at 54 months. To demonstrate the predictive contribution of the COTE to the BODE index, the survival curves were represented for each BODE score quartile(9) (Panel A BODE Q1 (score= 0,1,2), Panel B BODE Q2 (scores= 3,4), Panel C BODE Q3 (scores=5,6) and Panel D BODE Q4 (scores=7,8,9,10). In each panel patients were categorized as COTE score of 0 to 3 (blue line) or those ≥ 4 points (red line).

	COTE <4 (n)	COTE ≥ 4 (n)	Log-rank test
Panel A	505	90	<0.001
Panel B	367	103	<0.001
Panel C	233	79	<0.001
Panel D	214	68	0.02

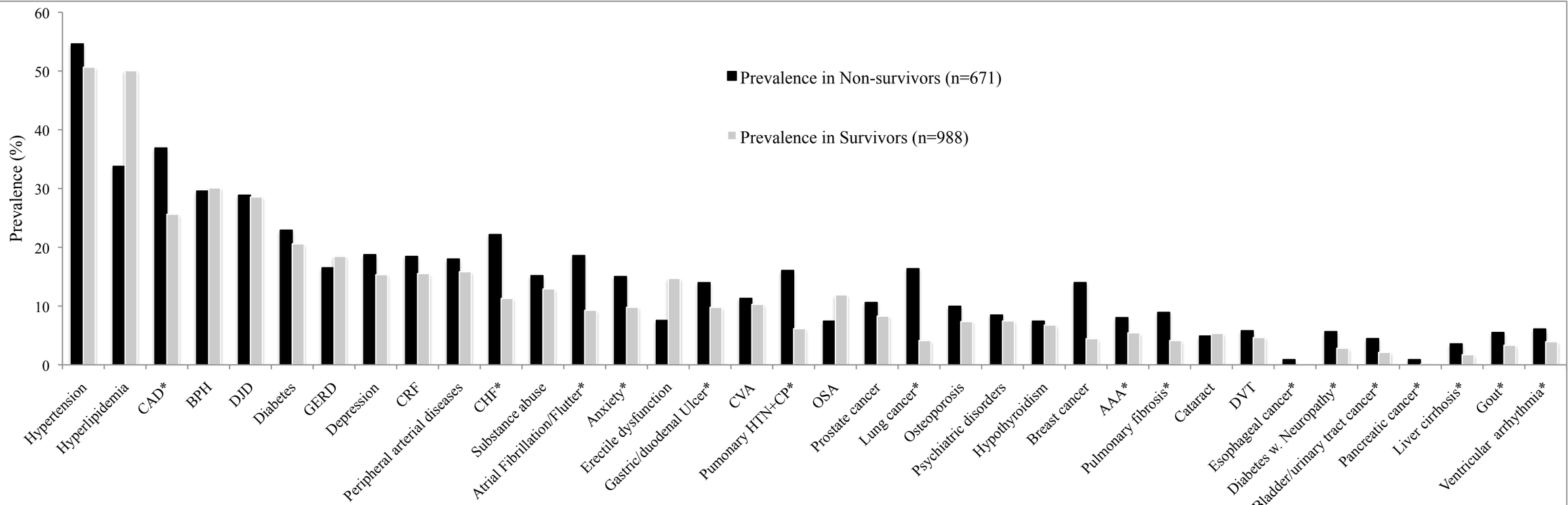
Table 1. Subjects' characteristics

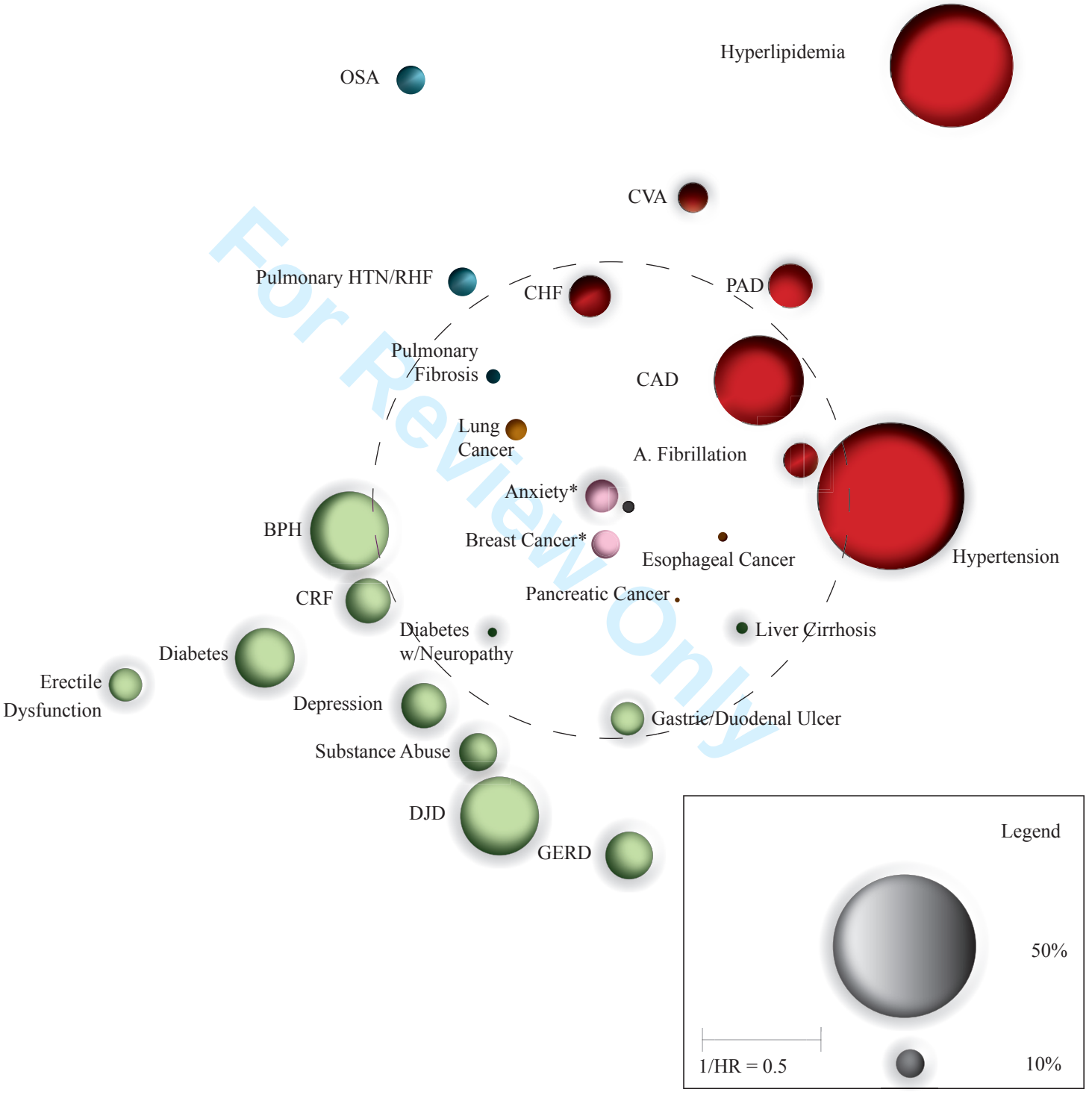
		Subjects included in analysis
Demographic		
	n	1659
	Age (mean±SD)	66 ± 9
	Male n (%)	1477 (89%)
Spirometry		
	FEV_1% (mean±SD)	49 ± 20
	GOLD I (%)	135 (8%)
	GOLD II (%)	593 (36%)
	GOLD III (%)	639 (39%)
	GOLD IV (%)	292 (17%)
BODE		
	BODE (mean±SD)	3.7 ± 2.6
	BODE 0,1,2 (%)	595 (36%)
	BODE 3,4 (%)	470 (28%)
	BODE 5.6 (%)	312 (19%)
	BODE 7,8,9,10 (%)	282 (17%)
Number of Comorbidities		
	Average +/- SD	6 +/- 3
	Range	0-21

Table 2. Comorbidities with the strongest association with increased risk for death.

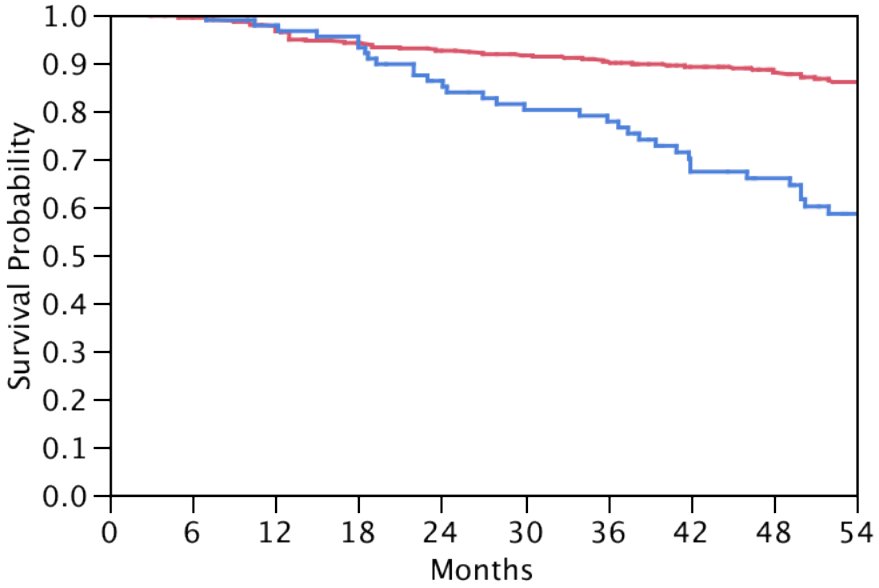
Comorbidity	Prevalence (%)	Hazard Ratio (95% CI)		p
Oncologic				
Lung Cancer	9.1	2.02	(1.63-2.51)	<0.001
Pancreatic cancer	0.4	2.72	(1.18-6.30)	0.02
Esophageal cancer	0.4	2.79	(1.15-2.79)	0.02
Breast cancer*	7.0	6.18	(1.07-35.68)	0.04
Pulmonary				
Pulmonary fibrosis	6.1	1.51	(1.13-2.03)	0.006
Cardiac				
Atrial Fibrillation/Flutter	13.0	1.56	(1.25-1.96)	<0.001
Congestive heart failure	15.7	1.33	(1.06-1.68)	0.02
Coronary artery disease	30.2	1.27	(1.06-1.54)	0.01
Gastrointestinal				
Gastric /duodenal ulcers	11.5	1.32	(1.05-1.66)	0.02
Liver cirrhosis	2.5	1.68	(1.07-2.65)	0.02
Endocrine				
Diabetes with neuropathy	4.0	1.54	(1.05-2.27)	0.03
Psychiatric				
Anxiety*	13.8	13.76	(2.13-88.63)	0.006

* Calculated on the female cohort and excluding male specific comorbidities from the multivariate analysis.

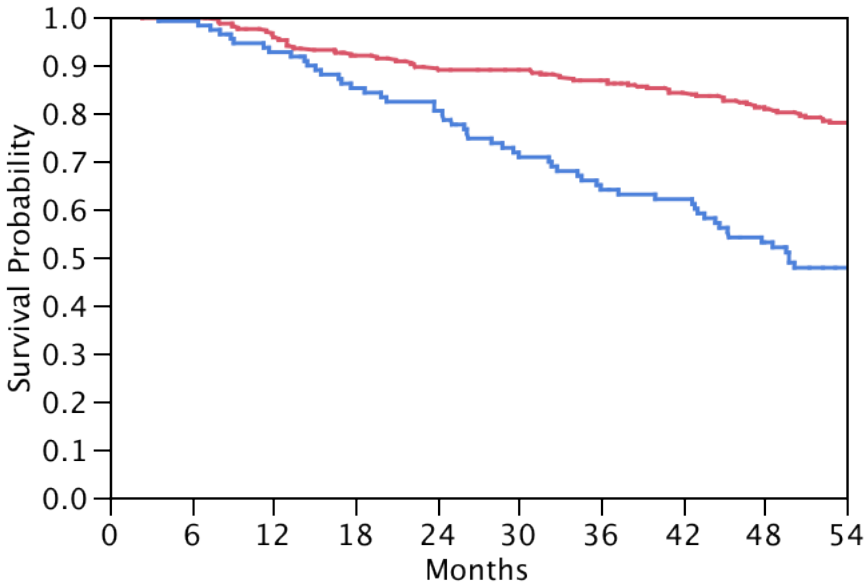

Prevalence (%)
60
50
40
30
20
10
0
Prevalence in Non-survivors (n=671)
Prevalence in Survivors (n=988)
Hypertension
Hyperlipidemia
CAD*
BPH
DJD
Diabetes
GERD
Depression
CRF
Peripheral arterial diseases
CHF*
Substance abuse
Atrial Fibrillation/Flutter*
Anxiety*
Erectile dysfunction
Gastric/duodenal Ulcer*
CVA
Pumonary HTN+CP*
OSA
Prostate cancer
Lung cancer*
Osteoporosis
Psychiatric disorders
Hypothyroidism
Breast cancer
AAA*
Pulmonary fibrosis*
Cataract
DVT
Esophageal cancer*
Diabetes w. Neuropathy*
Bladder/urinary tract cancer*
Pancreatic cancer*
Liver cirrhosis*
Gout*
Ventricular arrhythmia*



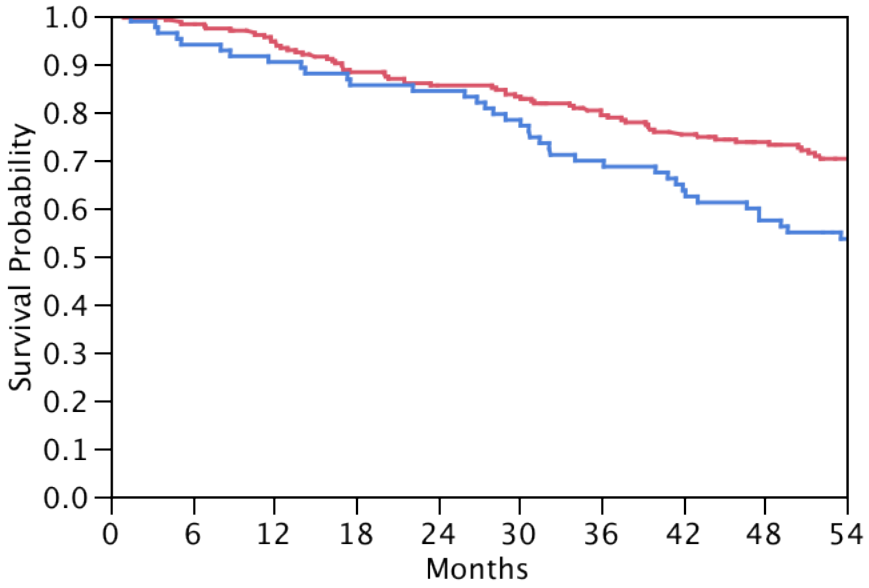
Panel A



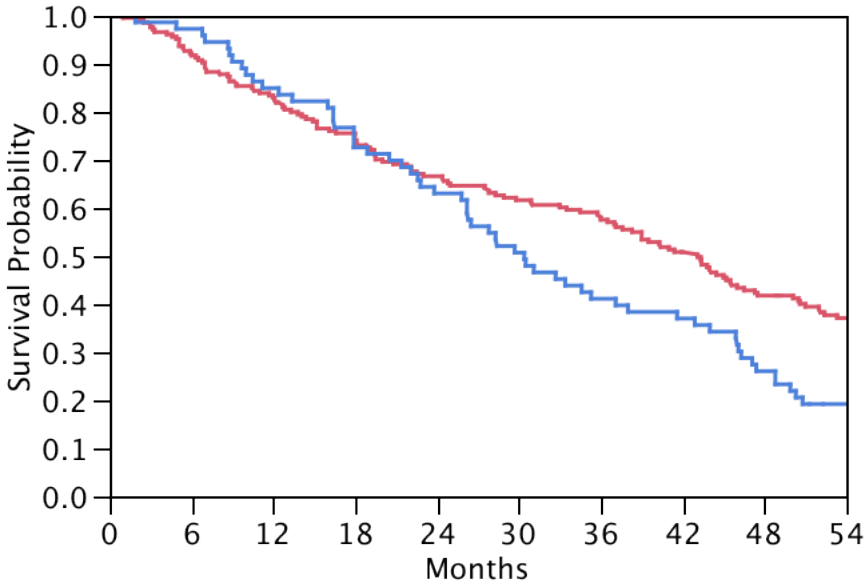
Panel B



Panel C



Panel D



Comorbidities and Risk of Mortality in Patients with COPD

Online-Supplemental Material

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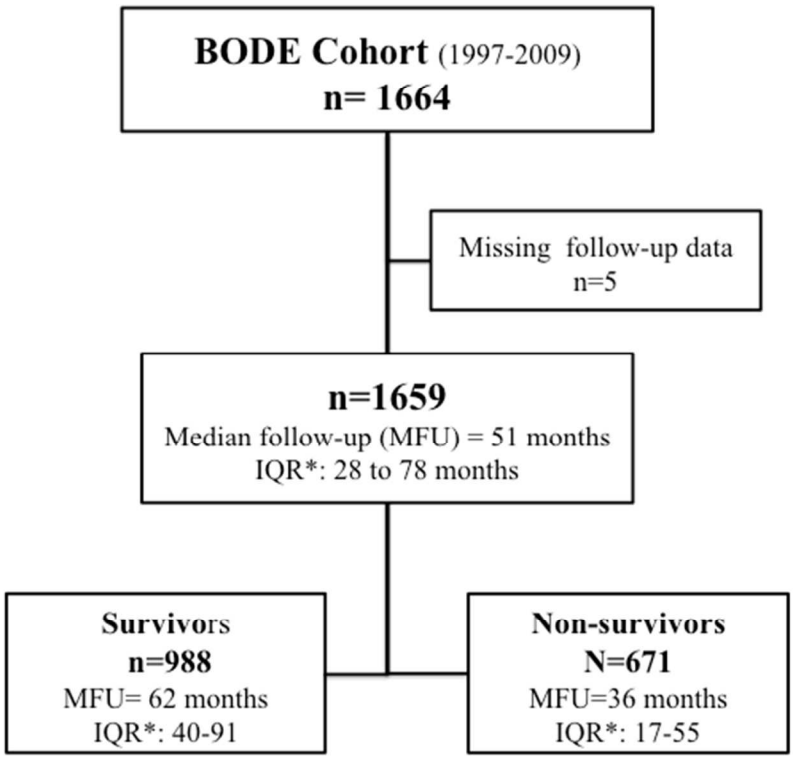
The BODE Collaborative Group

Material contained in this document: 3 Figures and 2 tables.

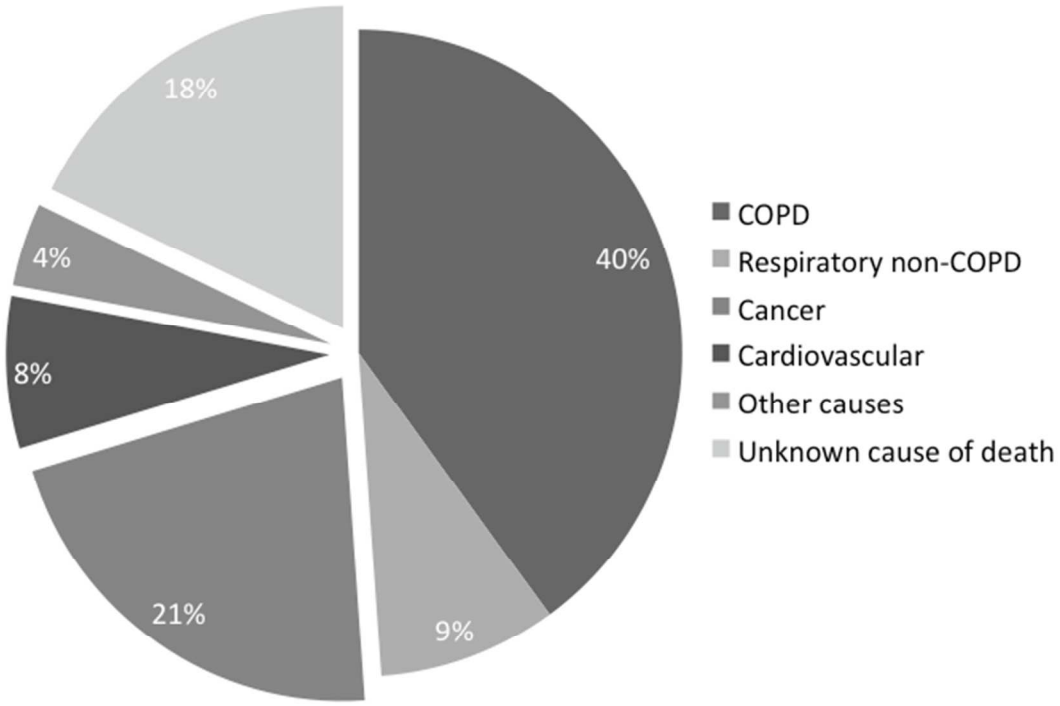
- Figure E1. Consort diagram describing recruitment of study participants and length of follow-up expressed in months.
- Figure E2. Cause specific mortality chart.
- Figure E3. Comorbidities presented in decreasing order of prevalence, partitioned by survivors and non-survivors.
- Table E1. Comorbidities prevalence for the full cohort and prevalence comparison between survivors and non-survivors
- Table E2. Comorbidities and Point Values Used for the Computation of COTE index.

Figure E1. Consort diagram describing recruitment of study participants and length of follow-up expressed in months.



*IQR: Interquartile Range

Figure E2. Pie chart representing the attributed cause of death for the 671 subjects who died during the follow up period. .



A specific cause of death was determined in 551 subjects (82% of all death). A category was then assigned using the same classification employed by the investigators in the TORCH study(1)

1. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in copd: Operations of the torch clinical endpoint committee. *Thorax* 2007;62:411-415.

Figure E3. Comorbidities presented in decreasing order of prevalence, partitioned by survivors (green bars) and non-survivors (red bars).

*Represent those comorbidities with a significantly higher prevalence in non-survivors compared to survivors (see Table E1 for details).

Abbreviations:

AAA= Abdominal Aortic Aneurism, BOOP= Bronchiolitis Obliterans with Organizing Pneumonia, BPH= Benign Prostatic Hypertrophy, CAD = Coronary Artery Disease, CHF=Congestive Heart Failure, CRF=Chronic Renal Failure, CVA=Cerebro-Vascular Accident, DJD= Degenerative joint Disease, DVT= Deep Venous Thrombosis, GERD=Gastro-Esophageal Reflux Disease, MAI=Mycobacterium Avium Infection, OSA= Obstructive Sleep Apnea, PAD: peripheral artery disease, Pulmonary HTN+RHF= Pulmonary Hypertension and Right Heart Failure.

Table E1. Comorbidities prevalence for the full cohort and prevalence comparison between survivors and non-survivors.

	Comorbidity	Prevalence full cohort (%)	Prevalence in survivors (%)	Prevalence in non-survivors (%)	p
1	Hypertension	52.3	50.7	54.6	0.12
2	Hyperlipidemia	43.5	50.1	33.8	<0.001
3	CAD *	30.2	25.6	36.9	<0.001
4	BPH	29.9	30.1	29.6	0.57
5	DJD	28.7	28.6	28.9	0.91
6	Diabetes	21.5	20.6	22.9	0.27
7	GERD	17.7	18.5	16.5	0.33
8	Peripheral arterial diseases	16.7	15.8	18.0	0.25
9	Depression	16.7	15.3	18.8	0.07
10	CRF	16.7	15.5	18.5	0.12
11	CHF*	15.7	11.3	22.2	<0.001
12	Substance abuse	13.8	12.9	15.2	0.19
13	Atrial Fibrillation/Flutter*	13.0	9.3	18.6	<0.001
14	Anxiety*	11.9	9.8	15.0	0.002
15	Erectile dysfunction	11.7	14.7	7.6	<0.001
16	Gastric/duodenal Ulcer*	11.5	9.8	14.0	0.008
17	CVA	10.7	10.3	11.3	0.51
18	Pumonary HTN+CP*	10.2	6.2	16.1	<0.001
19	OSA	10.1	11.9	7.4	0.003
20	Prostate cancer	9.3	8.3	10.6	0.056
21	Lung cancer*	9.1	4.1	16.4	<0.001
22	Osteoporosis	8.4	7.4	10.0	0.07
23	Psychiatric disorders not described elsewhere	7.9	7.5	8.5	0.45
24	Hypothyroidism	7.0	6.8	7.4	0.63
25	Breast cancer	7.0	4.4	14.0	0.56
26	AAA*	6.5	5.4	8.0	0.04
27	Pulmonary fibrosis*	6.1	4.1	8.9	0.001
28	Cataract	5.2	5.3	4.9	0.74
29	DVT	5.1	4.6	5.8	0.31
30	Gallbladder disease	4.9	5.1	4.6	0.65
31	Ventricular arrhythmia*	4.8	3.9	6.1	0.047
32	Glaucoma	4.4	4.3	4.5	0.90
33	Gout	4.2	3.3	5.5	0.03
34	Venous insufficiency	4.0	4.1	3.9	0.80
35	Diabetes w. Neuropathy*	4.0	2.8	5.7	0.005
36	History of tuberculosis	3.8	4.2	3.3	0.36
37	Hepatitis	3.8	4.6	2.5	0.026
38	Aortic Valve disorders	3.6	3.3	4.0	0.50
39	Nephrolithiasis	3.6	4.4	2.4	0.031

Table E1. Comorbidities prevalence for the full cohort and prevalence comparison between survivors and non-survivors. (Cont.)

40	Bladder/urinary tract cancer*	3.1	2.1	4.5	0.008
41	Connective Tissue disorders	2.8	2.5	3.1	0.54
42	Mitral Valve disorders	2.7	2.3	3.3	0.28
43	Dementia	2.6	2.1	3.3	0.16
44	Asbestosis	2.5	2.3	2.8	0.53
45	Liver cirrhosis*	2.5	1.7	3.6	0.023
46	Seizure	2.5	1.9	3.3	0.10
47	Bronchiectasis	2.2	3.6	0.1	<0.001
48	Pulmonary embolism	2.1	1.9	2.4	0.48
49	Pancreatitis	1.9	1.8	2.1	0.72
50	Head and Neck cancer	1.9	1.3	2.7	0.06
51	Colon cancer	1.9	1.5	2.4	0.20
52	Macular degeneration	1.3	1.0	1.6	0.27
53	Restless leg syndrome	1.2	1.2	1.2	1.0
54	Asthma	1.1	1.0	1.3	0.64
55	Melanoma	1.1	1.2	1.0	0.81
56	Hypogonadism	1.1	1.4	0.6	0.31
57	MAI	0.9	0.7	1.2	0.43
58	Leukemia	0.8	0.6	1.2	0.27
59	Parkinson's disease	0.8	1.0	0.6	0.42
60	Hyperthyroidism	0.8	0.8	0.9	1.0
61	Inflammatory Bowel disease	0.8	0.9	0.6	0.57
62	Sarcoidosis	0.7	0.9	0.3	0.21
63	Renal cancer	0.6	0.7	0.4	0.75
64	Alzheimer	0.5	0.6	0.4	0.75
65	Liver cancer	0.5	0.3	0.7	0.28
66	Pancreatic cancer*	0.4	0.1	0.9	0.02
67	Brain cancer	0.4	0.3	0.6	0.45
68	Esophageal cancer*	0.4	0.0	0.9	0.004
69	Thyroid cancer	0.3	0.2	0.4	0.39
70	Lymphoma	0.3	0.2	0.4	0.39
71	HIV	0.3	0.3	0.3	1.0
72	Alpha-1 deficiency	0.2	0.2	0.1	1.0
73	Testicular cancer	0.1	0.0	0.3	0.16
74	Tricuspid Valve disorders	0.1	0.1	0.1	1.0
75	Rectal cancer	0.1	0.0	0.3	0.16
76	Narcolepsy	0.1	0.2	0.0	0.51
77	BOOP	0.1	0.0	0.1	0.40
78	Broncholitis	0.1	0.1	0.0	1.0
79	Celiac disease	0.1	0.1	0.0	1.0

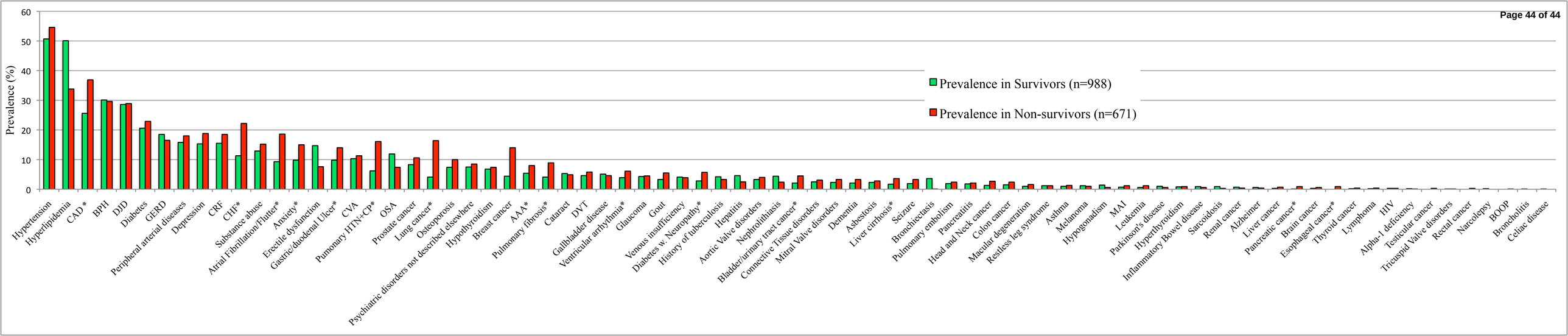
*Comorbidities with a significantly higher prevalence in non-survivors compared to survivors.
Abbreviations:

AAA= Abdominal Aortic Aneurism, BOOP= Bronchiolitis Obliterans with Organizing Pneumonia, BPH= Benign Prostatic Hypertrophy, CAD = Coronary Artery Disease, CHF=Congestive Heart Failure, CRF=Chronic Renal Failure, CVA=Cerebro-Vascular Accident, DJD= Degenerative joint Disease, DVT= Deep Venous Thrombosis, GERD=Gastro-Esophageal Reflux Disease, MAI=Mycobacterium Avium Infection, OSA= Obstructive Sleep Apnea, PAD: peripheral artery disease, Pulmonary HTN+RHF= Pulmonary Hypertension and Right Heart Failure.

Table E2. Comorbidities and Point Values Used for the Computation of COTE index.

Comorbidity	Hazard Ratio	Point assignment
Lung, esophageal, pancreatic and Breast* Cancer	>2.00	6
Anxiety*	13.76	6
All other cancers		2
Liver cirrhosis	1.68	2
Atrial Fibrillation/Flutter	1.56	2
Diabetes with neuropathy	1.54	2
Pulmonary fibrosis	1.51	2
Congestive heart failure	1.33	1
Gastric /duodenal ulcers	1.32	1
Coronary artery disease	1.28	1

Hazard Ratio <1.5 = 1, ≥1.5 = 2, and 6 for lung, pancreatic, esophageal and breast cancer, similar to the value assigned in the Charlson Comorbidity Index for metastatic cancer.
* Valid on the female population only.


Prevalence (%)
60
50
40
30
20
10
0
Prevalence in Survivors (n=988)
Prevalence in Non-survivors (n=671)
Hypertension
Hyperlipidemia
CAD *
BPH
DJD
Diabetes
GERD
Peripheral arterial diseases
Depression
CRF
CHF*
Substance abuse
Atrial Fibrillation/Flutter*
Anxiety*
Erectile dysfunction
Gastric/duodenal Ulcer*
CVA
Pumonary HTN+CP*
OSA
Prostate cancer
Lung cancer*
Osteoporosis
Psychiatric disorders not described elsewhere
Hypothyroidism
Breast cancer
AAA*
Pulmonary fibrosis*
Cataract
DVT
Gallbladder disease
Ventricular arrhythmia*
Glaucoma
Gout
Venous insufficiency
Diabetes w. Neuropathy*
History of tuberculosis
Hepatitis
Aortic Valve disorders
Nephrolithiasis
Bladder/urinary tract cancer*
Connective Tissue disorders
Mitral Valve disorders
Dementia
Asbestosis
Liver cirrhosis*
Seizure
Bronchiectasis
Pulmonary embolism
Pancreatitis
Head and Neck cancer
Colon cancer
Macular degeneration
Restless leg syndrome
Ashma
Melanoma
Hypogonadism
MAI
Leukemia
Parkinson's disease
Hyperthyroidism
Inflammatory Bowel disease
Sarcoidosis
Renal cancer
Alzheimer
Liver cancer
Pancreatic cancer*
Brain cancer
Esophageal cancer*
Thyroid cancer
Lymphoma
HIV
Alpha-1 deficiency
Testicular cancer
Tricuspid Valve disorders
Rectal cancer
Narcolepsy
BOOP
Bronchelitis
Celiac disease