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Sex differences between women and men with COPD: A new analysis of the 3CIA study

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Abstract:

Background: There is partial evidence that COPD is expressed differently in women than in men, namely on symptoms, pulmonary function, exacerbations, comorbidities or prognosis. There is a need to improve the characterization of COPD in females.

Methods: We obtained and pooled data of 17 139 patients from 22 COPD cohorts and analysed the clinical differences by sex, establishing the relationship between these characteristics in women and the prognosis and severity of the disease. Comparisons were established with standard statistics and survival analysis, including crude and multivariate Cox-regression analysis.

Results: Overall, 5,355 (31.2%) women were compared with men with COPD. Women were younger, had lower pack-years, greater FEV_1%, lower BMI and a greater number of exacerbations (all $p<0.05$). On symptoms, women reported more dyspnea, equal cough but less expectoration ($p < 0.001$). There were no differences in the BODE index score in women (2.4) versus men (2.4) ($p = 0.5$), but the distribution of all BODE components was highly variable by sex within different thresholds of BODE. On prognosis, 5-year survival was higher in COPD females (86.9%) than in males (76.3%), $p < 0.001$, in all patients and within each of the specific comorbidities that we assessed. The crude and adjusted RR and 95% C.I. for death in males was 1.82 (1.69-1.96) and 1.73 (1.50-2.00), respectively.

Conclusions: COPD in women has some characteristic traits expressed differently than compared to men, mainly with more dyspnea and COPD exacerbations and less phlegm, among others, although long-term survival appears better in female COPD patients.

Abstract word count: 250 words

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory condition characterized by chronic, progressive and mostly irreversible airflow limitation, associated with exposure to tobacco smoke, inhalation of occupational or environmental toxins or biomass combustion products[1,2]. COPD is a complex and heterogeneous disease associated with high morbidity and mortality. According to the latest update of the Global Burden of Disease Study, the prevalence of COPD in 2017 was 174 million people worldwide[3] and it was estimated that it became the third most common cause of death globally since 2012, after ischemic heart disease and cerebrovascular disease[4].

Population aging, a phenomenon more seen in women due to their longer longevity than men, and massive female uptake of smoking, has led to an increase in respiratory diseases associated with smoking in women, especially in the middle-aged, which has increased not only the prevalence, but also the associated morbidity and mortality. In the USA, COPD is already the leading cause of death among female smokers[5]. Since 2000, the number of women dying from COPD in the USA surpassed the number of men[6], and an assessment of mortality rates due to COPD showed a smaller decrease in the mortality rate among women with moderate or severe COPD than among men[7].

Despite this evidence, COPD is still considered mainly a “men's disease” by some clinicians, associated with a diagnostic bias that contributes to under-diagnosis in women[8]. Two similar studies, one conducted in the USA and Canada,[9] and the other in Spain[10], concluded that diagnosis of COPD was biased according to the sex of the patient. The results showed that given equivalent clinical conditions, men have a 1.5-fold chance of receiving a provisional diagnosis of COPD, a bias that is significantly reduced when abnormal spirometry results are available. Spirometry testing and referral to a pulmonologist are less common for women,[11] who suffer a significant delay in the diagnosis of COPD, explainable by voluntary postponement of access to

a consultation, or in some patients by the prevalence of symptoms of fatigue or depression that point to a different type of treatment.

Although data are limited, some studies have suggested that COPD is expressed differently in women than in men in relation to symptoms, pulmonary function, exacerbations or comorbidities[12,13,14,15] such that there is a need to improve the characterization of the disease in females in order to optimize the therapeutic approach of these patients. To address this issue, we obtained and pooled data of 17 139 patients from 22 COPD cohorts from seven countries and analysed the clinical differences of COPD by sex, establishing the relationship between these characteristics and the prognosis and severity of the disease.

METHODS

Study population

In this international study, we analysed patients from the COPD Cohorts Collaborative International Assessment (3CIA) initiative[16]. We obtained individual pooled data from 22 prospective cohort studies that systematically recruited patients with COPD in publicy-funded hospitals, except for the Copenhagen City Heart Study (CCHS)[17] and the HUNT study[18], which were population-bases studies. Details of each individual study have been published previously. All patients had a definition of COPD characterized by a post-bronchodilator ratio between the forced expiratory volume in the first second (FEV_1) and the forced vital capacity (FVC) of less than 0.7. Spirometry was performed using the standards provided by the American Thoracic Society and European Respiratory Society[19]. We obtained a minimum individual dataset including the vital status (up to death, right truncation or 2017), age, sex, smoking status, pre-bronchodilator and post-bronchodilator FEV_1 and FVC, and dyspnea measured with the modified Medical Research Council (mMRC) scale[20]. The primary investigators of each of the

participating 3CIA cohorts provided individual patient data for pooled analysis. All participants provided informed written consent, and each study was approved by the respective ethics committee.

We evaluated the study sample using prognostic parameters for COPD patients: age, dyspnea by mMRC scale, exercise capacity by the 6-min walk distance (6MWD), health-related quality of life by the Saint George's Respiratory Questionnaire (SGRQ) and BODE index score[21]. We also evaluated the presence of comorbidities by the Charlson index. Metabolic syndrome was defined as a cluster of three conditions: arterial hypertension, diabetes mellitus and obesity (BMI $\geq$ 30 kg/m^2). Participants were classified using the GOLD 2019 spirometric system into four grades (1-4) based on post-bronchodilator percent predicted FEV_1 as stage 1 ($FEV_1 \geq$ 80%), stage 2 (FEV_1 79%-50%), stage 3 (FEV_1 30%-49%) and stage 4 ($FEV_1 <$ 30%). Groups ABCD were defined by self-reported severity of dyspnea (mMRC) and severe exacerbations in the previous year[1].

3CIA was an observational study with variable follow-up. For the present analysis, follow up was censored five years after recruitment. During this follow up period, the principal investigators of each centre reported patient medical records, hospital admissions and deaths in a prospective manner.

Outcomes

The primary outcome was to better describe the clinical characteristics of women with COPD in a large international cohort of patients, evaluating the possible differential aspects of COPD versus men. Secondary outcomes were to analyse the mortality by all causes according to sex, as well as to evaluate the potential role of gender, among other variables, as a predictor of mortality in COPD.

Statistical analysis

The 3CIA database manager quality-controlled all data centrally and created a clean database with a data dictionary. All implausible or missing variables were queried with the original study investigators and removed the datum from the central database if errors could not be corrected. Because cohorts had different follow-up times, patients were censored at five years of follow-up.

Descriptive statistics used mean and standard deviation for continuous variables and counts with percentages for categorical variables. Comparisons between groups were performed with the chi-squared test for categorical variables and the ANOVA test for continuous variables. We estimated 5-year all-cause mortality by sex (total and by covariates), using Kaplan-Meier survival curves. We conducted both univariate and multivariate survival analyses based on the Cox proportional hazards model, using each of the potential predictors of mortality as independent variables and survival as the dependent variable. As per standard statistical practice, for the multivariate analysis, we only incorporated those variables significantly associated with mortality in the univariate analysis. Results were expressed as risk ratio (RR) with 95% confidence interval (CI). Alpha error was set at 0.05.

RESULTS

We pooled data from 22 COPD cohorts with a total of 17 139 patients. Table 1 shows demographic and clinical characteristics of patients by sex. Overall, 5,355 (31.2%) were women with a mean ± SD age of 62.1±10.1 years, significantly younger than men (65.0±10.2, $p < 0.001$). Women had lower pack-years (33.3 vs 47.8, $p < 0.001$), greater FEV_1 (% predicted) (60.9% vs 56.2%, $p < 0.001$), lower body mass index (BMI; 26.4 vs 27.0, $p < 0.001$), and a greater number of exacerbations in the last year (1.2 vs 1.0, $p = 0.008$). Regarding symptoms, women reported higher grades of dyspnea by the mMRC scale (1.8 vs 1.7, $p = 0.002$), equal cough ($p=0.407$) but less expectoration (37.2% vs 45.9%, $p < 0.001$). Distribution of patients classified by the GOLD 2019 staging system was sex-dependent, but no differences were found

in the BODE index score in women versus men (2.4 in both groups, p = 0.5). Selected co-morbidities, such as arterial hypertension and cardiovascular disease, quality of life (SGRQ) and some respiratory medications (LAMA or LABA or LABA + ICS), were also similar between sexes, all with p>0.05 (Table 1).

We then compared clinical and physiologic characteristics between women and men stratified by degree of airflow obstruction (FEV_1, % of predicted) (Table 2). Women with severe or very severe airflow limitation (< 50% FEV_1 of predicted) were significantly younger, less smokers and had lower BMI than men, all with p < 0.001. They also reported higher grades of dyspnea and had more co-morbidities evaluated by the Charlson index (2.6 vs 2.3, p = 0.003). No gender differences were found in the number of exacerbations in the last year in these patients. Similarly, in the subgroup of patients with more preserved pulmonary function (FEV_1 ≥ 50%), women also were younger, less smokers and presented a higher degree of dyspnea and worse nutritional status (BMI) than men; however, these women had less co-morbidities evaluated by the Charlson index (1.7 vs 2.4, p<0.001), a trend which was opposite to women with severe and very severe airflow limitation.

Figure 1 shows the relationship between BODE index score and its components [BMI, FEV_1 (% predicted), dyspnea (mMRC), 6MWD] by gender. Sex specific differences occurred in BMI at low BODE scores, MRC dyspnoea score in mid-range BODE scores (2-4), 6MWT distance at BODE scores ≤5 and FEV1 at BODE scores ≤6.

Figure 2 shows Kaplan-Meier curves for 5-year mortality (all-cause mortality) by sex and selected co-morbidities (asthma, arterial hypertension, diabetes mellitus, cardiovascular disease and metabolic syndrome). The Kaplan-Meier analysis showed that survival was significantly higher in females (86.9%) than in males (76.3%), p < 0.001. Survival remained better for women even when stratified by co-morbidities (asthma; 88.6% vs 83.1%, p < 0.001; cardiovascular comorbidities (hypertension, diabetes, cardiovascular disease or metabolic syndrome) all p<0.05), albeit with smaller differences than the whole group analysis.

Finally, Table 3 presents the crude relative risks of determinants of mortality, and a multivariate model with an adjusted analysis. As expected COPD mortality in COPD was increased in male, current-smokers, and was increased with mMRC, number of exacerbations, Charlson index and presence of all co-morbidities explored, except for asthma. In contrast, COPD mortality in COPD had a significantly inverse association with BMI, % predicted FEV1, and BMI. The most parsimonious multivariate model included sex, age and the single BODE components; as it can be seen, male sex was associated with increased mortality 1.73 (1.50-2.00) after adjustment.

DISCUSSION

Within this large, international study that includes a significant representation of women (31.2% of patients enrolled), we report that women with COPD develop a disease with a number of specific clinical characteristics, and better survival. Also, differences by sex occur in all four BODE components, especially in less severe COPD.

Several studies have previously reported sex-related differences in clinical manifestations of COPD, although our study has been carried out in a larger international cohort which brings both unprecedented precision and representativeness. Our results, aligned with previous publications[8,12,14,22], confirm that women with COPD were younger and require less cumulative smoking exposure than men. They presented a more symptomatic disease in terms of dyspnea, although they reported less sputum than males, with no differences in cough, as reported elsewhere[23]. Regarding co-morbidities, the concomitant diagnosis of asthma in women (25.8%) was more frequent than in men (19.5%) $p<0.001$. However, unlike the data obtained in the analysis of other cohorts, diabetes mellitus was more frequent in men, without significant differences in arterial hypertension or cardiovascular disease[14,24].

In terms of functional impairment, we saw that women had greater FEV_1 % than men. However, they had significantly worse exercise capacity (6MWD), lower BMI and higher

intensity of dyspnea (mMRC). Generally, for the same degree of airflow obstruction they were younger, less frequently current smokers, had lower BMI and higher dyspnea. Some studies suggest that other non-physiological factors, such as anxiety or depression, may be involved in the perception of dyspnea and should be systematically evaluated in female COPD patients[25].

In our study, we analysed the relationship between BODE index score and its components by sex. We found that women had better lung function (FEV_1%) than men with the same BODE score, as long as this score was not higher than 6 points (no sex-related differences in very severe patients). With regard to exercise capacity, on the other hand, women had lower 6MWD than men, except in patients with BODE score higher than 5 points (also very severe patients). In the case of nutritional status, women had lower BMI than men with the same BODE score, only in those cases with mild disease (BODE score less than 2 points). This evidence indicates that the differences by sex in either the contribution of each component of the BODE or in the total index score decrease as the severity of the disease increases, which is a novel finding. Since % predicted FEV_1, dyspnea score and exercise capacity each provide independent information regarding severity in patients with COPD, the multi-dimensional BODE index might have greater prognostic value in women with COPD than men[26]. Our data suggested that the proportional weight of each of the components of the BODE index varied by sex, dyspnea by the mMRC scale and BMI being the most important parameters in women[27].

In terms of survival, population-based studies show that universally females live longer than males, but COPD epidemiological studies suggest that mortality rates are declining faster in men than in women with COPD[7,28]. Indeed there are few clinical studies that determined sex-related differences in COPD survival, with contradictory results. Most of them included patients with severe disease and chronic respiratory failure[29,30,31,32], except for one based on a well phenotyped population with a wide range of COPD severity; this study showed that all-cause and respiratory mortality were lower in females than in males[26].

Our study results support a better survival of women with COPD compared to men (crudely and adjusted by demographic and clinical factors). Males were older, had greater smoking exposure and a higher Charlson index score than females, so all these factors could contribute to the sex differences in the mortality of these patients. In terms of prognosis, the study shows that, adjusted for all the significant prognostic variables, male sex remained an independent adverse prognostic factor. In fact, men had an adjusted all-cause mortality risk 1.73 times greater than women. Age and all four components of the BODE index also had an independent, deleterious effect on survival. Notably, the inverse association of BMI with mortality, both in the crude 0.98 (0.97-0.99), as well as the adjusted analyses 0.96 (0.95-0.97), further supports the so-called obesity paradox in COPD[33].

Our study has several limitations. Firstly, most of the patients were from hospital-based cohorts, and therefore may not represent the COPD population at large. Specifically, our study population could be affected by a well-described gender- bias in the diagnosis of COPD, which implies that women may, to some extent, be underrepresented. However, we do not consider that this fact distorts our findings or reduces its validity because our study includes a significant representation of women in a large cohort of patients with strict diagnostic criteria, which might be considered a strength. Secondly, only selected comorbidities were explored, so frequent diseases in women with COPD as anxiety, depression or osteoporosis were not objectively evaluated. Thirdly, the survival analysis evaluated all-cause mortality, as regrettably specific information about different causes of death was not collected consistently in all cohorts and participants.

To conclude, our results indicate that women with COPD were younger, less frequently smokers, and had better pulmonary function, but experienced more dyspnea and exacerbations. However, women with COPD had better survival than men. Our findings highlight the existence of significant sex-related differences in COPD risk and outcomes, supporting the importance of a better multidimensional approach to COPD in women.

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Table 1. Demographic and clinical characteristics of COPD patients, by gender

Characteristics	Women 5,355 (31.2%)	Men 11,784 (68.8%)	p value
Age (years)	62.1± 10.1	65.0 ± 10.2	< 0.001
BMI (kg/m^2)	26.4 ± 6.1	27.0 ± 5.0	< 0.001
Pack-year index	33.3 ± 25.6	47.8 ± 28.7	< 0.001
GOLD 2019 group			< 0.001
A	34.9%	39.4%	
B	41.0%	37.2%	
C	5.6%	6%	
D	18.5%	17.4%	
GOLD spirometric staging			< 0.001
1	20.0%	14.5%	
2	47.1%	44.1%	
3	23.3%	29.8%	
4	9.5%	11.6%	
Number of exacerbations in the last year	1.2 ± 1.7	1.0 ± 1.5	0.008
Dyspnea mMRC (points)	1.8 ± 1.4	1.7 ± 1.3	0.002
Cough	52.5%	50.8%	0.407
Sputum	37.2%	45.9%	< 0.001
FEV_1 *(% of predicted)*	60.9 ± 23.2	56.2 ± 21.9	< 0.001
6MWD	363.8 ± 120.2	396.3 ± 127.1	< 0.001
BODE index	2.4 ± 2.3	2.4 ± 2.1	0.503
SGRQ	38.9 ± 22.5	38.0 ± 21.9	0.098
Charlson index	2.1 ± 1.9	2.3 ± 2.0	< 0.001
Arterial hypertension	43.1%	43.1%	0.991
Diabetes mellitus	5.3%	11.2%	< 0.001
Cardiovascular disease	27.6%	29.9%	0.079
Asthma	25.8%	19.5%	< 0.001
Pharmacological treatment			

LAMA or LABA	20.1%	20.0%	0.349
LABA + LAMA	5.2%	7.7%	0.038
LABA + ICS	30.7%	30.5%	0.122
LABA+LAMA+ICS	44.0%	41.8%	0.014

Data are expressed as mean ± SD or %. Abbreviations: BMI, body mass index; GOLD, global obstructive lung disease; mMRC, modified medical research council; FEV_1, forced expiratory volume in the first second; 6MWD, 6-minute walk distance**;** BODE body mass index, degree of airway obstruction, dyspnea and exercise capacity by 6MWD; SGRQ, St. George's Respiratory Questionnaire; LAMA, long acting muscarinic antagonist; LABA, long acting Beta 2 agonist; ICS: inhaled corticosteroids

Table 2. Comparison of clinical and physiologic characteristics between women and men stratified by degree of airflow obstruction (FEV_1, % of predicted)

Clinical characteristics	$FEV_1 \geq 50\%$		p value	$FEV_1<50\%$		p value
	Women 3,584 (34.3%)	Men 6,879 (65.7%)		Women 1,755 (26.6%)	Men 4,851(73.4)	
Age (years)	61.6 ± 10.5	64 ± 10.5	<0.001	63.1 ± 9.3	66.5 ± 9.4	<0.001
BMI (kg/m^2),	26.7 ± 5.9	27.4 ± 4.8	<0.001	25.6 ± 6.4	26.4 ± 5.3	<0.001
Pack-years,	32 ± 25	45.3 ± 28.1	<0.001	35.4 ± 26.3	51.2 ± 29.2	<0.001
Charlson index,	1.7 ± 1.8	2.4 ± 1.9	<0.001	2.6 ± 1.9	2.3 ± 2	0.003
Number of exacerbations in the last year,	1.1 ± 1.6	0.7 ± 1.3	<0.001	1.3 ± 1.8	1.3 ± 1.6	0.674
Dyspnea mMRC (points), *n (%)*						
0-1	60.1%	65.2%	<0.001	22.7%	27.3%	<0.001
2-4	39.9%	34.8%		77.3%	72.7%	

Data are expressed as mean ± SD or %. Abbreviations: BMI, body mass index; mMRC, modified medical research council

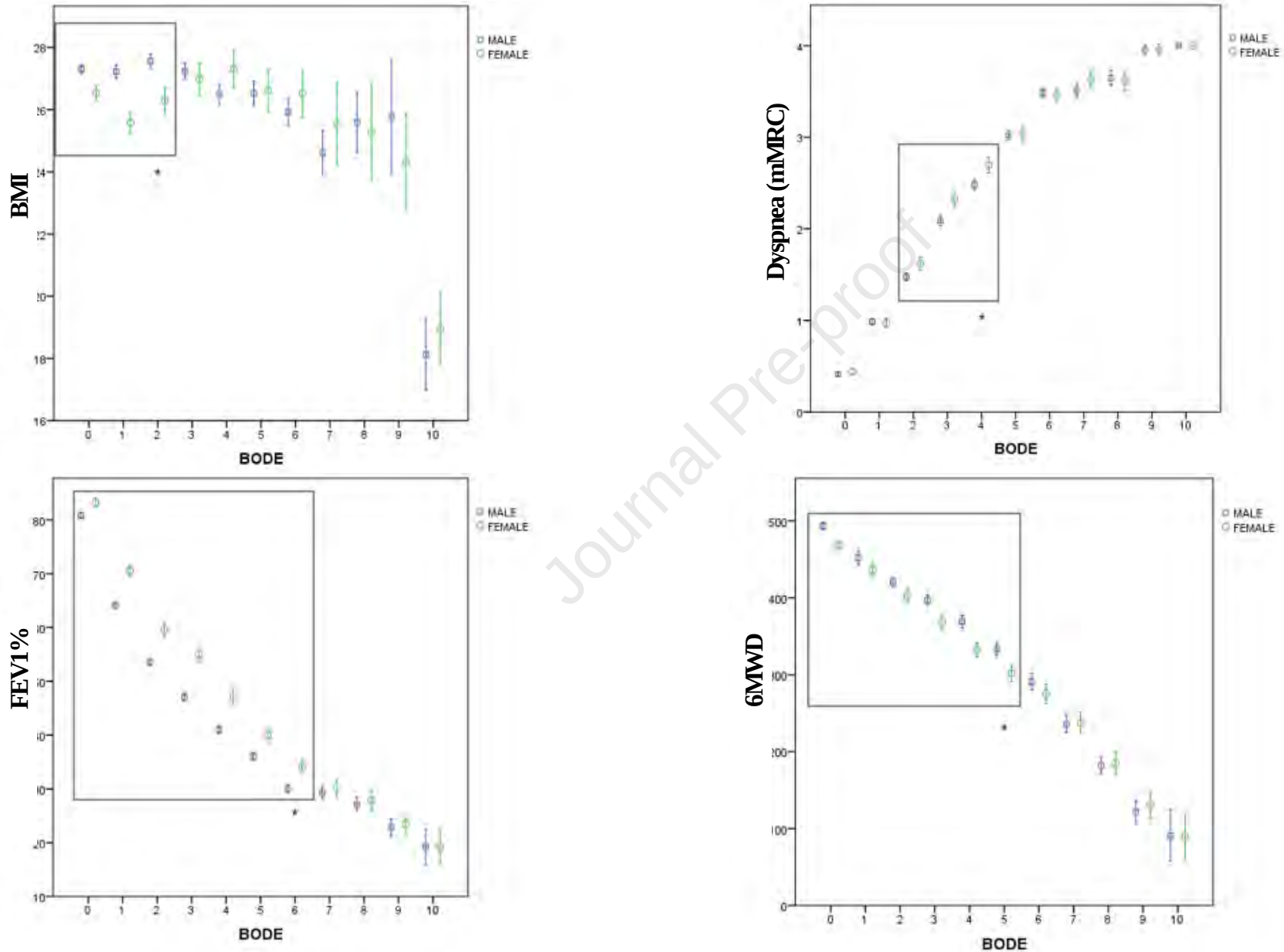
Table 3. Crude and multivariate analysis of predictors of mortality

	Crude RR and 95% C.I.	**Adjusted RR and 95% C.I.**
Sex, male	1.82 (1.69-1.96)	1.73 (1.50-2.00)
Age	1.07 (1.06-1.08)	1.04 (1.03-1.05)
Smoking status - Current - Former	 1.30 (1.14-1.49) 1.42 (0.76-2.64)	
BMI	0.98 (0.97-0.99)	0.96 (0.95-0.97)
% predicted FEV_1	0.97 (0.96-0.98)	0.98 (0.97-0.99)
mMRC	1.39 (1.36-1.42)	1.14 (1.08-1.21)
6-MWD	0.99 (0.99-0.99)	0.98 (0.97-0.99)
AECOPD	1.11 (1.07-1.14)	-
Charlson index	1.13 (1.10-1.15)	-
Hypertension	1.23 (1.041.46)	-
Diabetes	1.58 (1.35-1.86)	-
Cardiovascular Disease	1.32 (1.13-1.55)	-
Asthma	0.98 (0.88-1.09)	-

Note: *For the multivariate analysis, we only incorporated those variables significantly associated with mortality in the univariate analysis.*

Abbreviations: BMI: body mass index; 6-MWD: 6-minute walk distance; % predicted FEV_1: percent predicted forced expiratory volume in the first second; AECOPD: acute exacerbations of COPD; RR: relative risk

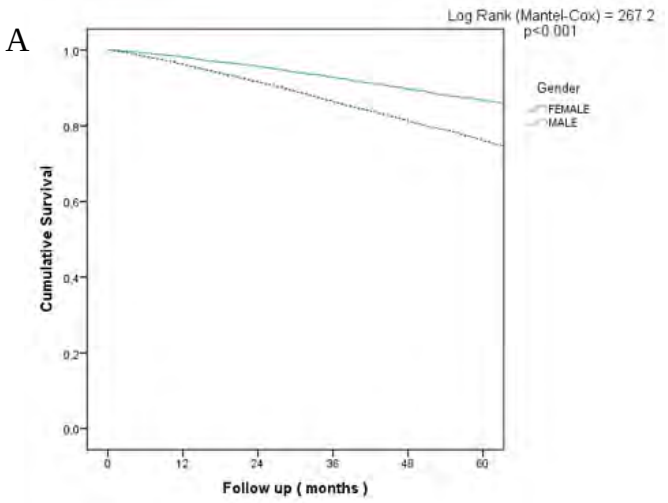
Figure 1. Relationship between BODE index score and its components [BMI, FEV1%, dyspnea (mMRC), 6MWD] by gender



Note: Data points represents mean value and 95% confidence interval. Framed areas (*) include those data points that show significant differences by gender ($p < 0.05$)
Abbreviations: BMI, body mass index; FEV1%, forced expiratory volume in one second; mMRC, modified medical research council; 6MWD, 6-minute walk distance

Figure 2. Five-year survival curves of COPD patients by gender in A) all; B) Asthma; C) Hypertension; D) Diabetes; E) Cardiovascular disease; and F) Metabolic Syndrome

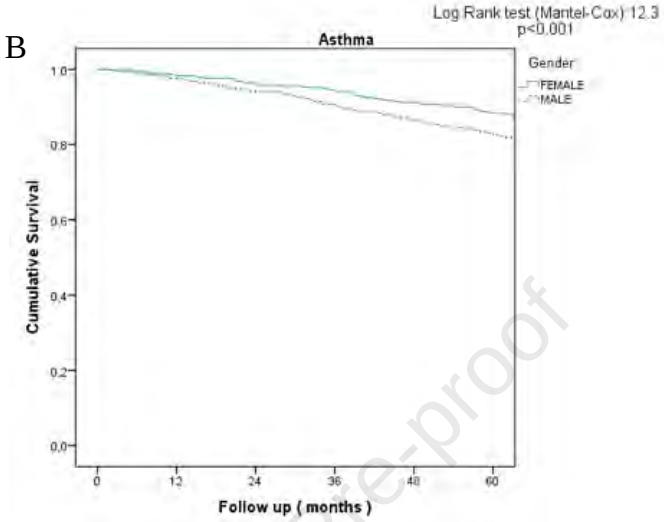
A



Patients at risk

FEMALE	5076	4872	4556	4083	2359	1745
MALE	11145	10500	9632	8645	5973	4813

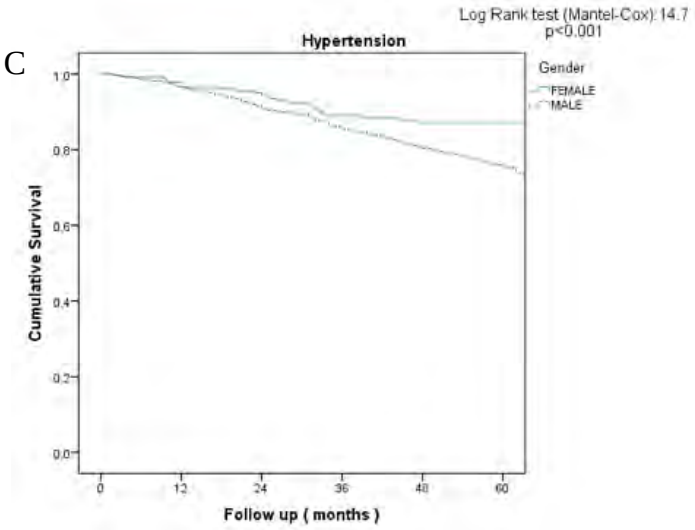
B



Patients at risk

FEMALE	574	557	529	513	382	366
MALE	835	806	759	721	578	542

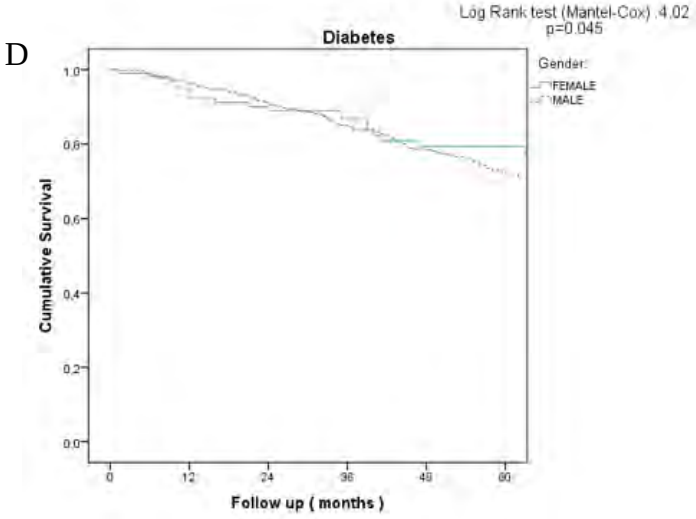
C



Patients at risk

FEMALE	243	221	181	153	138	127
MALE	888	826	708	625	551	449

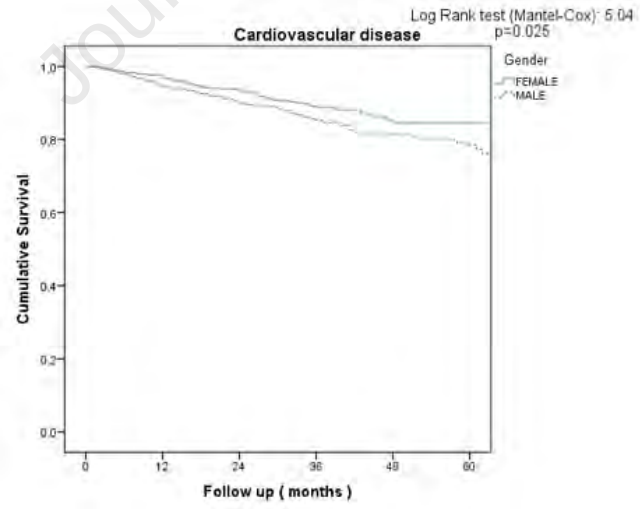
D



Patients at risk

FEMALE	105	96	83	78	51	49
MALE	484	454	402	356	268	226

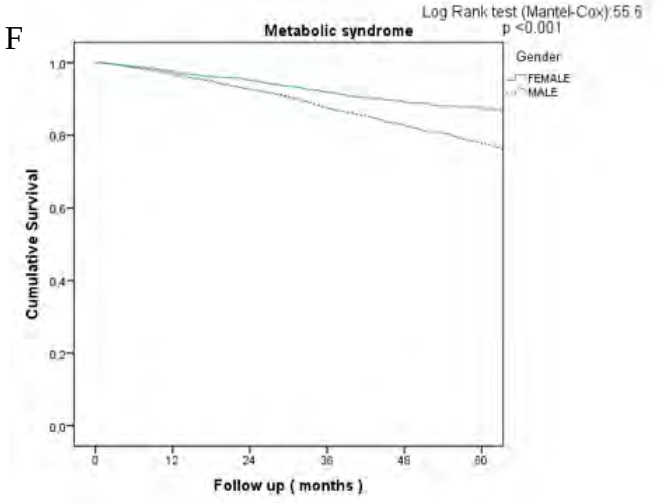
E



Patients at risk

FEMALE	474	461	434	402	97	92
MALE	1012	943	873	786	215	180

F



Patients at risk

FEMALE	1680	1595	1472	1302	709	521
MALE	4105	3878	3567	3179	2102	1680

HIGHTLIGHTS

- There are sex-related differences in COPD risk and outcomes.
- Women with COPD are younger, less frequently smokers and had better lung function, but experienced more dyspnea and more exacerbations.
- Our data suggest that the proportional weight of each of the components of the BODE index varied by sex.
- Women with COPD had better survival tan men.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: