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Gender Differences in Mortality in Patients with COPD

Juan Pablo de Torres MD[1,2], Claudia G Cote MD[3]

Maria V López MD[4], Ciro Casanova MD[2] , Orlando Díaz MD[5], Jose María Marin MD[6], Víctor Pinto-Plata MD[7], María Montes de Oca MD[8] , Hafida Nekach MD[3], Luis J Dordelly[3], Armando Aguirre- Jaime[2] and Bartolome R. Celli MD[7]

[1]Clínica Universitaria de Navarra, Pamplona, Spain

[2]Hospital Universitario Nuestra Señora de la Candelaria, Tenerife, Spain

[3]Bay Pines VA Health Care System, USA;

[4]Universidad de la República, Montevideo, Uruguay

[5]Departamento de Enfermedades Respiratorias, Pontificia Universidad Católica de Chile;

[6]Hospital Miguel Servet, Zaragoza, Spain

[7]Caritas St Elizabeth's Medical Center, Boston. Tutfs University. USA

[8]Hospital Universitario de Caracas, Venezuela

Drs de Torres and Cote contributed with the same effort in the completion of this study.

Corresponding author: Juan P de Torres MD

Pulmonary Department, Clínica Universitaria de Navarra, Pamplona Spain

Av. Pío XII, 36. Pamplona Spain 31008

Phone: 0034 948255400 Fax: 0034 948296500 Email: jupa65@hotmail.com

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ABSTRACT

Background: Little is known about survival and clinical prognostic factors in women with COPD.

Objectives: Determine the survival difference between men and women with COPD and compare the value of the different prognostic factors for the disease.

Methods: 265 women and 272 men with COPD matched at baseline by BODE and ATS/ERS/GOLD criteria were prospectively followed. Demographics, lung function, SGRQ, BODE index, its components and co-morbidity were determined. Survival was documented and gender differences were determined using Kaplan-Meier analysis. The strength of the association of the studied variables with mortality was determined using multivariate and receiver operating curves (ROC) analysis.

Results: All-cause (40% vs. 18%, $p< 0.001$) and respiratory mortality (24 % vs. 10%, $p<0.001$) were higher in men than women. Multivariate analysis identified the BODE index in women and the BODE index and Charlson co-morbidity score in men as the best predictors of mortality. The area under the curve (AUC) of the BODE index was a better predictor of mortality than the FEV_1% for both genders.

Conclusion: At similar COPD severity by BODE index and FEV_1%, women have significantly better survival than men. For both genders the BODE index is a better predictor of survival than the FEV_1.

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Short Running: Gender differences in mortality of COPD

INTRODUCTION

There is increasing evidence supporting gender differences in the clinical expression of COPD. Women seem to be more susceptible to the toxic effects of tobacco than men (1-5), They also report more anxiety and depression (6, 7), worse symptoms (8-10), lower exercise capacity (11), more airway hyper-responsiveness (12), and worse health related quality of life (HRQoL) (8, 11, 13, 14) than men. In a recent report by Martinez et al (8), women with severe emphysema enrolling in the National Emphysema Treatment Trial (NETT), smoked less, had a worse modified BODE index (mBODE), and lower DLCO% than their male counterparts. The pathological lung specimens of woman exhibited smaller airway lumens with disproportionately thicker airway walls, less extensive emphysema characterized by smaller hole size and less peripheral involvement than those of men. The same results were also reproduced by Dransfield et al (15). Whether or not the clinical differences in the expression of COPD in women result in different all cause and respiratory mortality compared to that of men remain unknown. The limited available information about gender differences in COPD mortality is derived from studies of patients with advanced stages of disease and hypoxemic respiratory insufficiency (16-19).

In this study we tested the hypothesis that women with similar degree of COPD severity (determined by the BODE index and by FEV_1%) have a different survival than men in a cohort of COPD patients with a wide range of airway obstruction from 5 different countries (USA, Spain, Chile, Venezuela and Uruguay). Additionally, we also tested the strength of the association between the baseline variables and mortality in the two genders.

METHODS

Patients

A total of 265 women with a wide range of COPD severity according to the American Thoracic Society (ATS), European Respiratory Society (ERS) (20), and the Global Initiative for Chronic Lung Disease (GOLD) (21), were sequentially recruited into the BODE observational study, between January 1997 and September 2006, at several clinics in the United States (Boston and Bay Pines, Florida), Venezuela, Chile, Uruguay and Spain (Tenerife, Pamplona and Zaragoza). As originally described, the BODE study (22) prospectively enrolled a cohort of well phenotyped patients with COPD irrespective of gender. Initially, few women were enrolled but over time more women participated. Once we achieved an appropriate number of female patients followed for at least 1 year we decided to retrospectively analyze the presence of gender differences in outcome. A total of 272 men from the same BODE cohort were matched by region and similar stage of COPD severity by BODE and ATS/ERS/GOLD. Special attention was given to include individuals enrolled during the same study period to avoid treatment differences over time. For example if a female COPD patient was enrolled in June 2000, a male COPD patient with similar FEV_1% and BODE index enrolled during the same year and region was selected for the matching process. The matched patients were obtained from an initial sample of 1115 males and 269 females with COPD. Every woman could be matched with a man with an FEV_1 % of predicted ± 5% and similar BODE index. To avoid selection bias, when more than one man was matched and they had a different BODE index, we decided to include both male patients with the same FEV_1. This event occurred in 7 patients. The 4 female patients who had no match were not included in the analysis. Inclusion and exclusion of these 11 patients do not affect the results. Participants were receiving standard medical treatment according to the ATS/ERS consensus (20). The human-research review board at

each site approved the study and all patients signed the informed consent. The inclusion/exclusion criteria have been previously published (22). Briefly, COPD was defined by a history of smoking at least 10 pack-years and a FEV_1/FVC ratio less than 0.7 measured 20 minutes after the administration of 400ug of inhaled albuterol. Patients were excluded if they had a history of asthma, bronchiectasis, tuberculosis or other confounding diseases like congestive heart failure, obliterative bronchiolitis or diffuse panbronchiolitis. The patients completed evaluation within six weeks of enrolment and continued to be followed thereafter until August of 2007 or until death. The patient and family were contacted if the patient failed to return for appointments. Death from any cause and from specific respiratory causes was recorded. The investigators at each site determined the cause of death after reviewing the medical record and death certificate. The cause of death was classified as respiratory if it was due to COPD, respiratory failure or respiratory tract infection; cardiovascular, lung cancer or others.

Measurements

Demographic and anthropometric information was collected. Spirometry, lung volumes and the six minute walking distance (6MWD) were performed following ATS guidelines (23,24). Dyspnea was assessed using the Modified Medical Research Council Dyspnea Scale (MMRC) (25). The body mass index (BMI) was calculated as the weight in kilograms divided by height in meters^2. The presence of co-morbidities was evaluated using the Charlson scale (26) where points are assigned to the presence of different co-morbidities. The score ranges from 0 to 37, with the higher the score implying more co-morbidities. Smoking status was expressed in pack-years. Inspiratory capacity (IC) was measured as previously described and IC/TLC was determined from the lung volume measurements (27). The BODE index was measured and staged in quartiles as previously

published (22). In short, the BODE index is a multidimensional grading system integrated by four variables: body mass index or BMI, (B), airflow obstruction (O) as measured by the post-bronchodilator FEV_1 (percentage of predicted value), dyspnoea (D) assessed by the modified Medical Research Council (MMRC) score, and exercise tolerance (E) measured by 6 minute walking distance. The variables were graded from 0 to 3 (0 or 1 for BMI) and added to provide a total score ranging from 0 to 10. A higher score indicates a greater risk of death and one point increase in the index represents a 34% and 62% increase in global and respiratory mortality respectively. The Saint George's Respiratory Questionnaire (SGRQ) was used to determine HRQoL (28) with the higher the index the greater health impairment and with 4 points representing a clinical significant difference (29).

Statistical analysis

Quantitative data with a normal distribution was described using mean ± SD. Qualitative data was described using relative frequencies. Survival times with all cause and respiratory mortality were determined. Differences between female and male deceased patients were assessed using Student t tests for independent sample or Pearson chi-square test, depending on variable characteristics. Kaplan–Meier analysis was used for comparison survival between men and women with similar COPD severity (BODE index and FEV_1%). The statistical significance was evaluated using the log-rank test. Cox Proportional Hazard Ratio analysis was performed to determine the best predictors of mortality in each gender, adjusting for those factors that showed differences between men and women: age, pack-years, co-morbidity and BMI. We include in the analysis all factors that have been shown to predict mortality in COPD patients: FEV_1%, 6MWD, MMRC, IC/TLC and the BODE index. To determine the relative predictive value for mortality of the BODE index

compared to the FEV_1%, C statistics was computed for a model containing FEV_1 or the BODE score as the sole independent variable. In these analyses, the C statistic is a mathematical function of the sensitivity and specificity of the BODE index and FEV_1% in classifying patients by means of the Cox model as either dying or surviving. The null value for the C statistic is 0.5, with a maximum of 1.0. The higher the AUC, the better the predictive power. Significant levels for all tests were established as two-tailed p-Value ≤ 0.05. Calculations were made with the statistical package SPSS version 15.0 Inc. (Chicago, IL, USA).

RESULTS

The baseline characteristics of the study patients by gender are shown in Table 1.

Similar number of men and women were recruited at all sites and there were no differences in any of the variables among regions (data not shown); therefore the data is presented as a group. A total of 265 women and 272 men with COPD were included in the study. The patients were followed for a mean of 49 ± 28 months. FEV_1% ranged between 10% and 94% of predicted value. There were 14% COPD patients in stage I, 31% in stage II, 37% in stage III, and 18% in stage IV according to ATS/ERS/GOLD. Conversely, 36% were in BODE Q1, 33% in Q2, 19% in Q3 and 12% in Q4.

Table 1 shows that at similar degree of airflow obstruction, there were differences between men and women in age, smoking status, pack-years history, co-morbidity, BMI and SGRQ.

Mortality

A total of 141 patients died during the follow up period (26.2%). The mean follow up time from enrolment to death was 34 ± 21 months for the group, 39 ± 22 for females and 32 ± 20 for males. A total of 97 patients (69% of the non survivors) were male. Seventy-six patients (54%) died due to respiratory causes during the study period. Mortality at each center was higher in men than in women.

The characteristics of non survivor male and female patients are shown in Table 2 A and B. For all cause mortality, non survivor females were very similar to males except for a lower BMI and lower tobacco consumption in pack-years. The BODE index and the Charlson co-morbidity

indexes, were similar in both genders (Table 2A). Survivors and non-survivor were similar in all parameters for respiratory deaths (Table 2B B).

Figure 1 shows all cause and respiratory mortality in non survivor male and female by BODE quartiles. Women had significant lower all cause mortality than men in all quartiles. Respiratory mortality was similar in all BODE quartiles except Q4 where it was higher in men.

The Kaplan Meier analysis (Figure 2) showed that survival was significantly higher in women than men with similar BODE index and FEV_1 ($p<0.001$).

Univariate and Multivariate analysis

The predictive power for all cause and respiratory mortality of the variables selected, adjusted for age, pack-years history, Charlson and BMI are shown in Table 3. The upper panel shows the results of the univariate analysis whereas the lower panel shows the final result of the multivariate analysis, which included all factors that showed significance in the univariate analysis again adjusted for the same parameters. The BODE index was the only variable associated with all cause mortality for women, whereas for men the model included the BODE index and Charlson co-morbidity score. The model explained a higher percentage of the variance for females compared with males (32.5% vs. 16.8 %, $p<0.001$). The BODE index was also the only variable associated with respiratory mortality for both genders. This model explained a higher percentage of the variance (46 %) in women.

ROC analysis

The discriminatory value of the BODE index in relation to survival was significantly higher than that of FEV_1% in both genders (Figure 3).

DISCUSSION

This study has two important findings. First, women with similar degree of airflow obstruction and BODE index have better survival over time than men. Second; the BODE index predicts all cause and respiratory mortality in women as well as it does in men.

In population based studies, women live longer than men (30-32). Recent epidemiological studies suggest an increased mortality rate in women with COPD (33,34). However, there are very few clinical studies attempting to determine gender related differences in COPD survival adjusting for variables known to predict outcome. Four previous studies on highly selected patients with chronic respiratory failure and hypoxemia have specifically addressed mortality differences between men and women. Three studies (16-18) indicated that women with COPD have a better prognosis than men, whereas one concluded the opposite (19). Miyamoto et al. (16) studied 9759 patients with COPD, TB sequelae or chronic interstitial pneumonia receiving long term oxygen therapy (LTOT) and reported a better survival for women than men. Crockett et al (17) studied a population of 505 COPD patients (256 females) also on LTOT and confirmed those previous findings. They also reported that the prognostic factors for females (age, FEV_1, BMI and comorbidities) were different from those of men (only BMI). Recently, Franklin et al (18), followed 5689 (2894 women) COPD patients on LTOT and after adjusting by age also found a better survival in women. Interestingly, the authors noted that the incidence and prevalence for LTOT increased more rapidly in women than in men. All of these reports supported a better survival in women than in men with severe COPD. In contrast, Machado et al (19) assessed 435 patients (184 women) with severe COPD receiving LTOT and followed them over time. Surprisingly, the risk of death whether adjusted by

age, smoking history, PaO_2, FEV_1 and BMI, was higher in women than in men. Our results support a better survival of women compared to men with similar baseline severity of airflow obstruction or BODE.

There are important differences between our and these previous studies. First, while the previous reports included patients with severe disease and chronic respiratory failure requiring LTOT, our study is based on a well phenotyped population of patients with a wide range of COPD severity. The majority of patients included in our study had either mild or moderate COPD (Stage 1 or 2 in the GOLD classification) and in Q1 ad Q2 of the BODE index. Second, previous studies adjusted the results by some prognostic factors but not by the best predictor of mortality in COPD: the BODE index (22).

In the current study, men were slightly older, had a longer smoking history and a higher co-morbidity score than women, all factors that may play a role in the survival difference between men and women. However, the difference in mortality persisted after adjusting for these factors (table 3), which suggests the presence of other reasons not detected by the Charlson co-morbidity index. This suggests a need to develop a better index that can more precisely capture the co-morbidities of importance in patients with COPD. Although the impact of co-morbidities in the clinical course of COPD was described almost a decade ago (35), it is only now that it has begun to receive specific attention (36). In this study, co-morbidities seemed to impact only in all cause mortality in men (Table 3). Surprisingly, when we compared respiratory mortality by BODE quartiles, a higher mortality in men than in women was found only in the most severe quartile. This is an important finding that reproduces those reported by Celli et al (22) and Incalzi and co-workers (35), which suggests that the course of COPD per se, may be similar in women and men

as the COPD progresses and that the differences in overall survival in the men with more severe COPD could possibly be due to added co-morbidity. This could also explain the differences in all cause mortality between both genders. From our study, it is difficult to exactly determine if the type of co-morbidities is the same for males and females because the overall Charlson score, although higher in men, failed to reach statistical significance. We could speculate that the increased mortality in men is due to a higher prevalence of cardiovascular disease and lung cancer in this gender, but this remains to be explored.

The multidimensional BODE index (22) was developed and validated in a cohort of patients with COPD that consisted primarily of men (95%). BODE was a better predictor of outcome than the GOLD stages in two different studies (37, 38). The current study expands these observations showing that the BODE index predicts survival in women as well as in men and that for both genders the BODE index is a better predictor than FEV_1%. The multivariate analysis showed that BODE index is an excellent predictor of all cause and respiratory mortality for women and men. Interestingly, we have previously reported, that the relative weight of each individual component of the BODE index differs between men and women (39). However, the composite index prognosticates with similar power in both genders. This finding makes the BODE index very useful when comparing gender related outcomes because it provides a global comprehensive overview not provided by the individual domains. Our data supports the usefulness of the BODE index as a tool to assess the multidimensional expression of the disease irrespective of gender.

Our findings have some clinical implications in the management of women with COPD. Given the better survival for women with the higher BODE scores (7 to 10), interventions such as lung

volume reduction surgery or lung transplantation could be timed differently. For example, if a COPD patient in BODE quartile 4 is evaluated for lung transplant, the evaluating team should be aware that the 3 year survival time for women is approximately 50% while only 20% for men. Likewise, a more aggressive detection and treatment of co-morbidities is suggested in men, as they are likely to be the cause of death in this gender.

There were some limitations to this study. First, our patients were enrolled in pulmonary clinics in Europe, Latin America and the US; therefore, the findings may not be totally applicable to the entire worldwide COPD population. However, this study represents the largest study of well phenotyped women with COPD using the most important prognostic factors for the disease. Second, although we were careful to match male and female patients that were enrolled during the same study period, we can not be entirely sure that differences in mortality are not due to treatment differences. However, none of the currently available treatments for the disease have shown to be gender sensitive (40). Thirdly, the exact proportion of the causes of death may not be accurate since it was obtained from review of the medical records or death certificates. This is a known limitation of many COPD survival studies (41). However, the primary outcome of the study was to investigate gender differences in all cause mortality, a very hard end-point. Fourthly, we acknowledge the important impact that exacerbations have in mortality of COPD patients. Unfortunately, we did not have precise information in some study sites thus preventing a robust analysis of the data. Finally, we did not evaluate depression and anxiety in this cohort. However, these tend to be worse in women (42) and would if anything impact more on women than in men.

In summary, this study shows that all cause and respiratory mortality are significantly lower in women than in men with similar COPD severity. It also shows that the BODE index is as good a predictor of mortality in women as in men with COPD. Larger studies are needed to further investigate gender influence in the expression of COPD.

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Table No. 1: Baseline characteristics of patients in the cohort.

VARIABLES	Male n= 272	Female n= 265	p Value*
Age (years)	67± 8	63 ± 10	<0.001
Current smoking %	32	44	0.005
Tobacco use (pack/Year)	81 ± 43	51 ± 29	<0.001
Charlson's index (points)	3.8 ± 2.6	2.7 ± 2.4	<0.001
BODE Index (points)	3.49 ± 2.5	3.37± 2.1	0.55
MMRC (points)	2.0 ± 1.1	2.11 ± 0.9	0.5
6MWD (meters)	392 ± 138	392 ± 103	0.9
BMI (kg/m^2)	26.8 ± 5	25.7 ± 5	<0.01
FEV_1 (% predicted)	49 ± 20	50 ± 19	0.87
FVC (% predicted)	74 ± 22	78.7 ± 23	0.05
FEV_1/FVC (%)	46 ± 13	48.8 ± 12	0.06
IC/TLC (%)	32 ± 1	30 ± 1	0.05
SGRQ Total	44 ± 21	48 ± 19	0.04

*** Comparison between male and female**

BODE= Body Mass Index (BMI); Obstruction (FEV_1); Dyspnea (MMRC); Exercise Capacity (6MWD). FEV1= Forced Expiratory Volume in 1 Second; MMRC= Modified Medical Research Council Dyspnea Scale; 6MWD= 6-Minute Walking Distance. FVC= Forced vital capacity. TLC= Total lung capacity. IC= Inspiratory capacity. SGRQ= Saint George´s respiratory Questionnaire.

Table 2 A: Baseline characteristics of male and female patients who died from any cause during the study period.

VARIABLES	Male n= 97	Female n = 44	P Value*
Age (years)	70 ± 8	68 ± 8	0.19
Current smoking %	30	35	0.64
Tobacco use (pack/Year)	90 ± 38	70 ± 40	<0.001
Charlson's index (points)	4.75 ± 2.9	3.8 ± 2.6	0.08
BODE Index (points)	4.9 ± 2.6	5 ± 1.7	0.69
MMRC (points)	2.64 ± 0.9	2.48 ± 0.8	0.34
6MWD (meters)	305 ± 135	292 ± 108	0.58
BMI (kg/m^2)	26 ± 5	23.7 ± 5	0.03
FEV_1 (% predicted)	44 ± 19	39 ± 14	0.16
FVC (% predicted)	67± 19	69 ± 21	0.61
FEV_1/FVC (%)	44 ± 13	44± 13	0.99
IC/TLC (%)	28 ± 1	27 ± 1	0.40
SGRQ Total	52 ± 19	58 ± 16	0.11

*** Comparison between males and females.**

Table 2 B: Baseline characteristics of male and female patients who died from respiratory causes during the study period.

VARIABLES	Male n= 55	Female n = 21	P Value*
Age (years)	68 ± 8	67 ± 9	0.88
Current smoking %	57	32	0.05
Tobacco use (pack/Year)	86 ± 41	69 ± 40	0.86
Charlson's index (points)	4.8 ± 3	4.0 ± 2	0.81
BODE Index (points)	5.0 ± 2.7	5.1 ± 1.7	0.86
MMRC (points)	2.8 ± 0.9	2.5 ± 0.8	0.96
6MWD (meters)	300 ± 139	285 ± 115	0.14
BMI (kg/m^2)	26 ± 6	23.5 ± 5	0.08
FEV_1 (% predicted)	42 ± 18	39 ± 14	0.08
FVC (% predicted)	73 ± 23	67 ± 19	0.93
FEV_1/FVC (%)	43 ± 13	42 ± 13	0.86
IC/TLC (%)	28 ± 12	27 ± 9	0.38
SGRQ Total	55 ± 21	58 ± 15	0.47

*** Comparison between males and females.**

BODE= Body Mass Index (BMI); Obstruction (FEV_1); Dyspnea (MMRC); Exercise Capacity (6MWD). FEV1= Forced Expiratory Volume in 1 Second; FVC= Forced vital capacity; MMRC= Modified Medical Research Council Dyspnea Scale; Charlson: Charlson comobidity score; 6MWD= 6-Minute Walking Distance. TLC= Total lung capacity. IC= Inspiratory capacity. SGRQ= Saint George´s respiratory Questionnaire.

Table 3. Cox Proportional Hazard Ratio analysis to investigate the predictive power for mortality of each of the selected variables in males and female patients with COPD.

Univariate analysis

Outcome	Variable		Hazard Ratio	Confidence Interval (95%)	p value
All cause Mortality	FEV_1%	Males	0.98	0.97 to 0.99	0.01
		Females	0.93	0.90 to 0.97	<0.001
	6MWD	Males	0.99	0.98 to 0.99	<0.001
		Females	0.99	0.98 to 0.99	<0.001
	MMRC	Males	1.89	1.50 to 2.38	<0.001
		Females	2.11	1.17 to 3.79	0.01
	IC/TLC	Males	0.01	0.002 to 0.20	0.001
		Females	0.91	0.83 to 0.99	0.04
	BODE	Males	0.93	0.90 to 0.97	<0.001
		Females	1.65	1.31 to 2.07	<0.001
Respiratory Mortality	FEV_1%	Males	0.98	0.96 to 0.99	0.01
		Females	0.99	0.98 to 0.99	<0.001
	6MWD	Males	0.99	0.98 to 0.99	<0.001
		Females	0.99	0.98 to 0.99	<0.001
	MMRC	Males	2.24	1.68 to 2.97	<0.001
		Females	2.48	1.32 to 4.68	0.005
	IC/TLC	Males	0.01	0.01 to 0.31	0.006
		Females	0.01	0.00 to 0.77	0.04
	BODE	Males	1.35	1.21 to 1.50	<0.001
		Females	1.74	1.36 to 2.23	<0.001

Analysis adjusted for age, pack-years history, comorbidity , BMI.

Multivariate analysis including all variables significant in the univariate analyisis

Outcome	Group	variable	Hazard Ratio	Confidence Interval (95%)	p value
All cause Mortality	Females	BODE	2.26	1.6 to 3.2	<0.001
	Males	BODE	1.4	1.21 to 1.61	<0.001
		Charlson	1.19	1.03 to 1.37	0.032
Respiratory Mortality	Females	BODE	3.17	1.87 to 5.36	<0.001
	Males	BODE	1.53	1.30 to 1.79	<0.001

Analysis adjusted for age, pack-years history, comorbidity , BMI.

BODE= Body Mass Index (BMI); Obstruction (FEV_1); Dyspnea (MMRC); Exercise Capacity (6MWD). Charlson: Charlson comorbidity score; Saint George´s respiratory Questionnaire (SGRQ)

Figure 1.

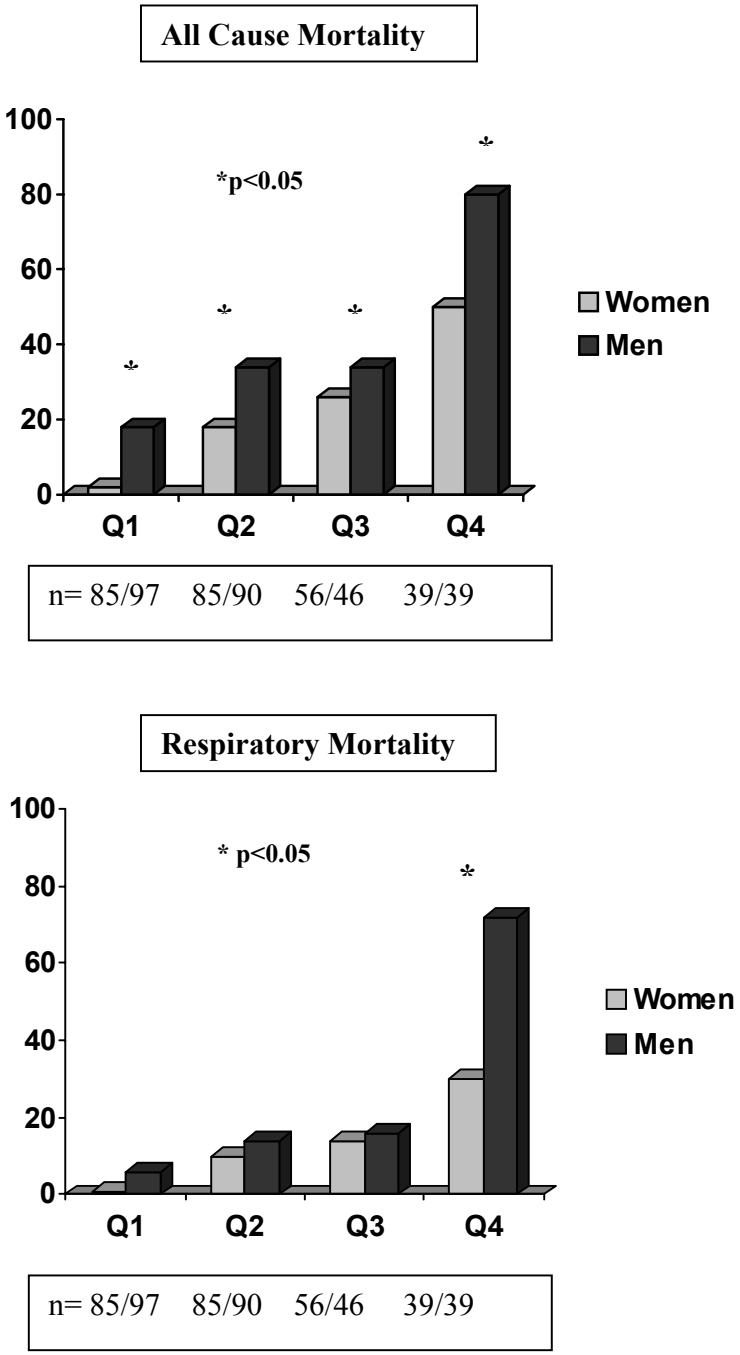

All Cause Mortality
100
80
60
40
20
0
*p<0.05
Q1
Q2
Q3
Q4
Women
Men
n= 85/97 85/90 56/46 39/39
Respiratory Mortality
100
80
60
40
20
0
* p<0.05
Q1
Q2
Q3
Q4
Women
Men
n= 85/97 85/90 56/46 39/39

Figure 2.

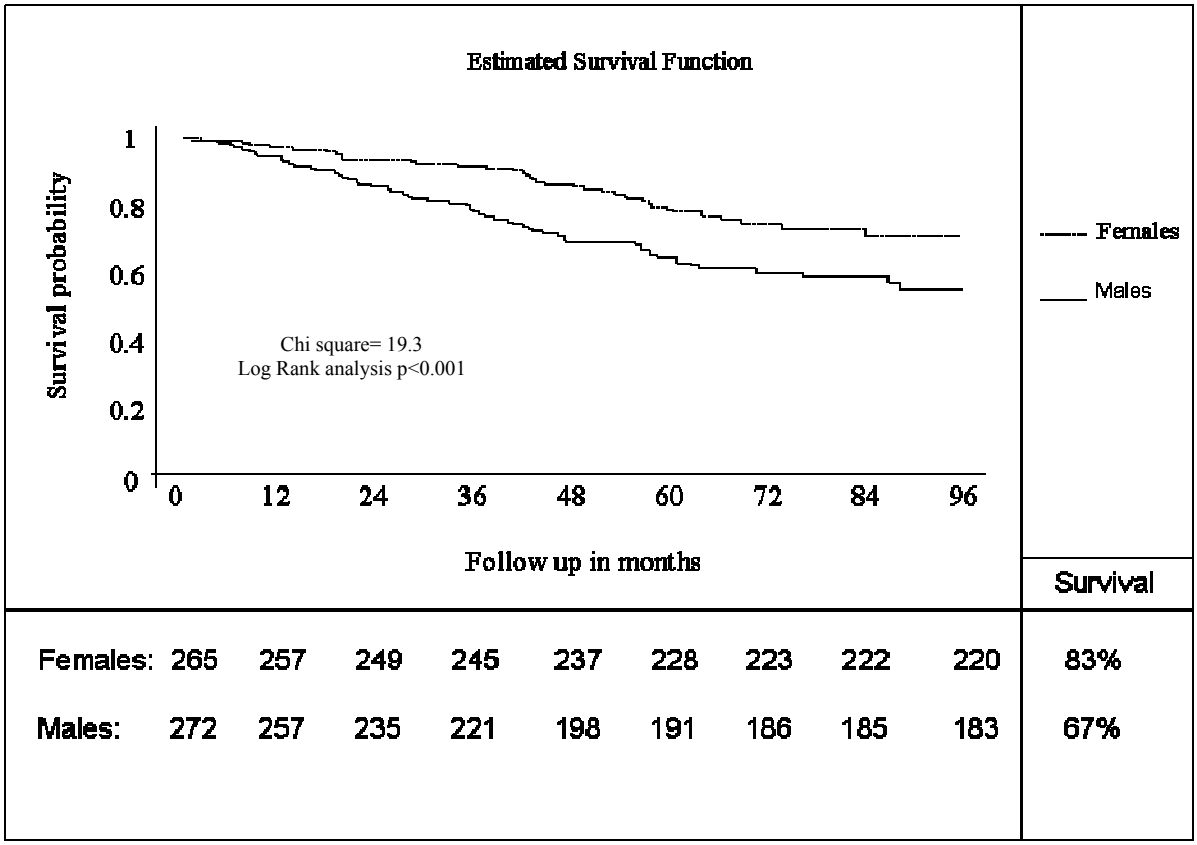
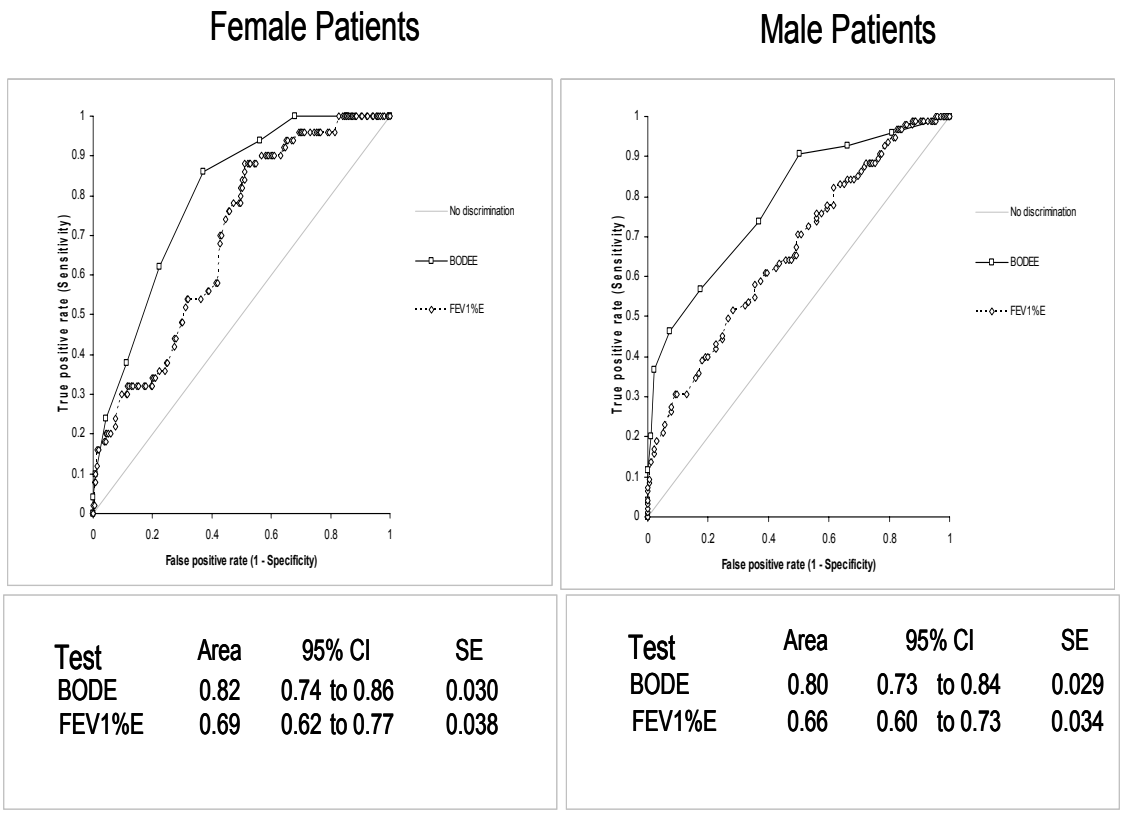

Estimated Survival Function
Survival probability
1
0.8
0.6
0.4
0.2
0
Chi square= 19.3
Log Rank analysis p<0.001
0
12
24
36
48
60
72
84
96
Follow up in months
Females
Males
Survival
Females: 265 257 249 245 237 228 223 222 220 83%
Males: 272 257 235 221 198 191 186 185 183 67%

Figure 3.



Test	Area	95% CI	SE
BODE	0.82	0.74 to 0.86	0.030
FEV1%E	0.69	0.62 to 0.77	0.038

Test	Area	95% CI	SE
BODE	0.80	0.73 to 0.84	0.029
FEV1%E	0.66	0.60 to 0.73	0.034

Legends to figures:

Figure 1: All cause mortality and respiratory mortality are represented in the superior and inferior panels respectively by BODE quartiles. Significant differences were found in all quartiles for all cause mortality and in the Q4 for respiratory mortality. The x axis represent each quartile of the BODE index and the y axis the percentage of patients in each quartile.

Figure 2: Kaplan Meier survival curves of the study population by gender. Log rank analysis shows that survival is better for the female population.

Figure 3: Receiver Operating Curves for all cause mortality for the BODE Index and FEV1 % in men and women with COPD. The discriminative values of the BODE index was higher than the discriminative value for FEV1 % in both females and males.