Finding the Best Thresholds of FEV$_1$ and Dyspnea to Predict 5-Year Survival in COPD Patients: The COCOMICS Study

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Abstract

Background: FEV$_1$ is universally used as a measure of severity in COPD. Current thresholds are based on expert opinion and not on evidence.

Objectives: We aimed to identify the best FEV$_1$ (% predicted) and dyspnea (mMRC) thresholds to predict 5-yr survival in COPD patients.

Design and Methods: We conducted a patient-based pooled analysis of eleven COPD Spanish cohorts (COCOMICS). Survival analysis, ROC curves, and C-statistics were used to identify and compare the best FEV$_1$ (%) and mMRC scale thresholds that predict 5-yr survival.

Results: A total of 3,633 patients (93% men), totaling 15,878 person-yrs. were included, with a mean age 66.4±9.7, and predicted FEV$_1$ of 53.8% (±19.4%). Overall 975 (28.1%) patients died at 5 years. The best thresholds that spirometrically split the COPD population were: mild ≥70%, moderate 56–69%, severe 36–55%, and very severe ≤35%. Survival at 5 years was 0.89 for patients with FEV$_1$ ≥70 vs. 0.46 in patients with FEV$_1$ ≤35% (HR: 6; 95% CI: 4.69–7.74). The new classification predicts mortality significantly better than dyspnea (mMRC) or FEV$_1$ GOLD and BODE cutoffs (all p<0.001). Prognostic reliability is maintained at 1, 3, 5, and 10 years. In younger patients, survival was similar for FEV$_1$ (%) values between 70% and 100%, whereas in the elderly the relationship between FEV$_1$ (%) and mortality was inversely linear.

Conclusions: The best thresholds for 5-yr survival were obtained stratifying FEV$_1$ (%) by ≥70%, 56–69%, 36–55%, and ≤35%. These cutoffs significantly better predict mortality than mMRC or FEV$_1$ (%) GOLD and BODE cutoffs.

Introduction

According to the Global Burden of Disease Study, in 2010 chronic obstructive pulmonary disease (COPD) was the third leading cause of death worldwide and the ninth combining the years of life lost or lived with disability (DALYs). COPD is characterized by an airflow limitation and therefore spirometry remains the essential test to diagnose the disease. Classically, COPD severity has been graded by postbronchodilator FEV$_1$ expressed as percent of predicted values (FEV$_1$ %). More recently, several multidimensional indices have shown a better survival prediction than the isolated FEV$_1$ (%). These include the original BODE index, which incorporates dyspnea measured with the modified scale of Medical Research Council (mMRC), Body Mass Index (BMI), FEV$_1$, and exercise capacity assessed with the 6-minute walking distance (6MWD), as well as further modifications of this index, such as the BODEx (replacement of exercise capacity with severe exacerbations). Other multidimensional prognostic indices are ADO (age, dyspnea, and FEV$_1$), SAFE
(quality of life measured by Saint George’s Respiratory Questionnaire, FEV1, and 6MWD), and DOSE (dyspnea, smoking status, FEV1, and prior exacerbation history), among others.[7–9]

These indices have been constructed by adding different variables – such as dyspnea, exercise capacity, exacerbations, and age – to different categories of FEV1 values.[10] However,
different thresholds of FEV₁ and dyspnea are used in different staging systems and with different guidelines.[11–12] To date, the most widely used cutoff values are those proposed by the Global Obstructive Lung Disease (GOLD) and the ATS/ERS guidelines (mild $<80\%$, moderate 50–79\%, severe 30–49\% and very severe $<30\%$).[13] However, the BODE index uses the old ATS standards ($<65\%$, 50–64\% 36–49\% and $<35\%$), while the DOSE index uses a different cutoff (50–59\%, 30–49\% and $<30\%)$.[4,9] To the best of our knowledge the majority of these classifications are selected arbitrarily, based on cut-offs selected by expert opinion, and it is not known which of them best discriminates among different levels of mortality risk. Additionally, there are few studies comparing the usefulness of FEV₁ in different age groups and the influence of dyspnea on survival assessment.[14–16]

The aim of the present study was to identify the best thresholds for FEV₁ (%) and dyspnea measured with the mMRC to predict 5-yr survival in COPD patients, divided by subsets of age, using a pooled-analysis of individual patient data from eleven Spanish COPD cohorts (The COllaborative COhorts to assess Multicomponent Indices of COPD in Spain-COCOMICS study).[10]

Table 2. Area under the curve (AUC) to predict 1, 3, 5, and 10-yr survival at different staging spirometry thresholds, dyspnea levels (mMRC) and time.

<table>
<thead>
<tr>
<th>YEARS</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>COCOMICS</td>
<td>0.643</td>
<td>0.650</td>
<td>0.657</td>
<td>0.654</td>
</tr>
<tr>
<td>GOLD</td>
<td>0.635</td>
<td>0.639</td>
<td>0.647</td>
<td>0.639</td>
</tr>
<tr>
<td>Old ATS (BODE)</td>
<td>0.643</td>
<td>0.650</td>
<td>0.653</td>
<td>0.649</td>
</tr>
<tr>
<td>mMRC (Dyspnea)</td>
<td>0.623</td>
<td>0.620</td>
<td>0.625</td>
<td>0.614</td>
</tr>
<tr>
<td>P</td>
<td>0.013</td>
<td>0.006</td>
<td>0.004</td>
<td>0.006</td>
</tr>
</tbody>
</table>

GOLD: Global Obstructive Lung Disease classification. ATS: American Thoracic Society classification. BODE: Body Mass Index, Obstruction (measured with old ATS classification), Dyspnea and Exercise. mMRC: Dyspnea measured with the modified Medical Research Council scale.

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Methods

Ethics Statement

All participants gave their informed written consent to participate, and their respective ethics committees approved each study (Hospital Galdeakao-Usarsolo, Navarra Clinic University Hospital, Requena Hospital, Uninary Hospital Mútua de Terrassa, University Hospital of Valme and University Hospital Miguel Servet).

Study design

The COCOMICS study is a pooled-analysis of individual patient-data from eleven Spanish COPD patient cohorts. The methodology has been described in detail elsewhere.[10,17] Briefly a common data set with age, gender, spirometry, comorbidity, previous severe exacerbations, and follow-up among other variables was provided by the principal investigator of each of the participating cohorts.[6,18–26] Previous severe exacerbations were defined as those requiring emergency room visit with or without subsequent hospitalization during the previous year. All-cause mortality at 5 years was defined as the primary outcome. Postbronchodilator forced spirometry was performed according to the guidelines of the American Thoracic Society/European Respiratory Society consensus.[27] Dyspnea was assessed using mMRC dyspnea scale.[5] Comorbidities were quantified by means of the Charlson index, excluding COPD, without adjustment for age.[28] All cohorts were previously published although with different follow-up periods; the references of original articles are available in the Online Appendix. All data were quality controlled centrally, and a homogeneous template to translate all coding was applied.

Statistical analysis

Qualitative variables were expressed as absolute and relative frequencies, while quantitative variables were summarized as mean and standard deviation in the case of symmetry, and median otherwise. Comparison among continuous variables was made using the robust means comparison Student-Welch test, under symmetry, and the non-parametric Mann-Whitney U test otherwise. The Fisher exact test was used in order to check independence among categorical variables. We focused all analyses on time to death for all causes. Standard Cox semi-parametric
The free software R 2.15 was used for developing the computation and then, on each one of the two resulting sub-populations of a first stage, the threshold which leads to the Youden index was computed for maximizing the AUC at five years follow-up. In a second stage of the analysis, the goodness-of-fit quality of the considered models was measured using the area under the incidence/dynamic ROC curve [30], AUC. The R package risksetROC, freely available in the R CRAN (www.r-project.org), was used for developing the computations. All the comparisons between the curves were performed using the L1-measure (given two functions, f and g, the L1-measure is defined by $L_1(f,g) = \int |f(t) - g(t)| \, dt$). The general Bootstrap Algorithm (gBA) [31] was used in order to approximate the respective P-values. The gBA method allows developing complex hypotheses preserving the original data structure and without assuming any additional hypothesis (just the one considered null). Finally, optimal % FEV1 and dyspnea thresholds were computed for maximizing the AUC at five years follow-up. In a first stage, the threshold which leads to the Youden index was computed and then, on each one of the two resulting sub-populations and with the same criteria, a new threshold was computed. In all analyses, P-values below 0.05 were considered for statistical significance. The free software R 2.15 was used for developing the analysis.

Results

A total of 3,633 subjects with COPD (93% men) were included in the analysis, totaling the experience of 15,678 person-years. The mean age was 66.4 (SD ±9.7). At study entry, smoking exposure was substantial (53.4±26.5 pack-years), with 71.0% former smokers, and 27.9% current smokers. Most participants had moderate to severe airflow limitation with a predicted FEV1 (%) of 53.8±19.4%, and a Charlson index of 2.1±1.5. Patients over 65 had significantly more comorbidities measured with the Charlson index than young people (≤64 years) [1.83 (1.44) vs. 2.17 (1.60); p<0.0001].

The main characteristics of the population cohorts are presented in Table 1. On average women were younger (59.8±11.0 years vs. 66.9±9.5 years) and more frequently current smokers (43.3% vs. 26.8%) than men (both p<0.05). After 5 years, 975 (28.1%) subjects had died. A significantly greater mortality was observed in older patients and women. Lower levels of FEV1 (%) and BMI, greater dyspnea, poorer quality of life measured with the Saint George’s Respiratory Questionnaire (SGRQ), shorter distance walked in 6 x’ walking-test, and severe exacerbations of COPD during the previous year were also associated with a statistically significant five-year increased mortality (Table 1).

Mortality during short, medium and long-term follow-up – from one to 10 years - was consistently associated with FEV1 (%) (Figure 1, Table 2). The best FEV1 thresholds (%) in the entire cohort to predict 5-year mortality were mild ≥70%, moderate 56–69%, severe 35–55%, and very severe ≤35%. Figure 2 shows graphically the risk of mortality at the different cutoffs of FEV1 (%). Of note, patients with an FEV1 (%) lower than 35% had a hazard ratio (HR) for mortality that was 6 times higher than the reference group with FEV1≥75% [95% Confidence Interval (CI): 4.69–7.74].

The probability of survival at 5 years was 0.89 (95% C.I.:0.86–0.92) in patients with higher levels of FEV1 (%) (>70%) in contrast to 0.46 (95% C.I.:0.42–0.51) for patients with FEV1 (%) <35%. Kaplan-Meier curves for different thresholds of FEV1 (%) and 5-year mortality in the present study compared with GOLD and old ATS-BODE cutoffs are displayed in Figure 3.

For all comparisons, the predictive ability of the new cutoff points was higher than that of the previous cutoffs used in the GOLD document and slightly better than those used in the BODE index (old ATS). Hazard Ratios and their 95% CI between the different cutoffs of the COCOMIX study, GOLD, and BODE are presented in Table 3. prognostic reliability of new thresholds is maintained at 1, 3, 5, and 10 years (Table 2).

The prognostic value of FEV1 (%) differed according to age. In patients 65 or older, we observed an inverse progressive
relationship between mortality and lung function, while in individuals younger than 64, mortality was similar in the interval of FEV1% between 75% and 100%.

Among patients with lower levels of dyspnea (mMRC\textless{}=1), overall survival at 5 years was 75.6% (95% CI: 73.2–78.1), for those who also had lower dyspnea an FEV1 (%) >90% survival at 5 years was 92.1% (95% CI: 86.5–98.1). In contrast, patients with higher levels of dyspnea (mMRC\textgreater{}=2) had a 5-year survival of 56.0% (95% CI: 53.3–58.9). No differences existed in the predictive ability of FEV1 (%) by gender. The relationship between FEV1 (%), age, gender and dyspnea are graphically displayed in Figure 4.

Of note, comparisons between Kaplan-Meier curves for the different levels of FEV1 (%) and dyspnea (Figure 5) showed that FEV1 (%) was a significantly better predictor of survival than degree of dyspnea (\textit{p}<0.001). Similarly, the new cutoffs of FEV1 (%) were significantly better predictors of survival at 1, 3, 5, and 10 years than the levels of dyspnea measured with the mMRC (Table 3) (Figure 5).

Discussion

The current study was conducted in a large sample of patients over the entire spectrum of COPD severity with long-term follow-up, and it shows that the proposed new spirometric thresholds to predict 5-year mortality (mild\textgreater{}=70%, moderate 56–69%, severe 35–55%, and very severe \textless{}=35%) were significantly better predictors of survival than those used in the GOLD, and slightly better than those used in the BODE index (old ATS). This improvement in predictive capacity was also verified in both the short- and long-term follow-up (1 to 10 years). The study design – a pooled-analysis of individual patient-data from several cohorts – the large sample size and the different degrees of severity of the patients in the different cohorts guarantee a high external validity of the results.

Traditionally, lung function, measured with the FEV1 after a bronchodilator test, has been the most widely recognized variable associated with mortality in COPD. Furthermore, FEV1 is a good predictor of mortality even in the general population, and it is also considered the most important variable to evaluate the severity of COPD.[32] In addition, the decline in FEV1 over time has been used to evaluate the progression of the disease, although wide individual variability exist.[33] Until the last decade, different scientific societies and clinical guidelines had proposed different thresholds of postbronchodilator FEV1 expressed as percentage of predicted values to classify the severity of the disease. However these cutoffs were selected for pragmatic and educational reasons based on expert opinion, which explains the existing discrepancies

Figure 4. Spline inverse of the 5-yr hazard ratio for FEV1 and death, adjusted for: A) age, B) gender and C) dyspnea.
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Figure 5. Kaplan-Meier survival curves up to five years for different thresholds of A) FEV1 according to new COCOMICS and B) mMRC. The quality of the models is measured from the AUC in the incidence/dynamic ROC curves.FEV1 is a better predictor of 5-year survival (\textit{p}<0.005).
doi:10.1371/journal.pone.0089866.g005
in the proposed values.[3,11] To the best of our knowledge, the present study is the first in which the different recommended thresholds were obtained from a cohort study looking for improved sensitivity and specificity points validated for mortality.

One important observation of our study is that although patients with lower levels of FEV$_1$ (<35%) had a mortality that was 6 times higher than the patients with better FEV$_1$ (>75%), 5-year survival of patients with worse FEV$_1$ (%) is almost 50%. In other words, higher values of FEV$_1$ are associated with lower mortality, but a low FEV$_1$, even below 35% predicted, does not exclude prolonged survival. These data are consistent with previous studies and highlight the conclusion that isolated FEV$_1$ should not be used as an exclusive predictor of prognosis.[23,34]

Accordingly, the new multicomponent indices have shown better predictive capacity for survival than FEV$_1$ alone. The two common variables included in all multidimensional prognostic indices in COPD are respiratory function – measured with postbronchodilator FEV$_1$ (%)– and dyspnea.[4,6,7,9] However the cutoffs used are COPD are respiratory function – measured with postbronchodilator FEV$_1$ values.

COCOMICS includes many more patients with a wider range of thresholds were obtained from a cohort study looking for predictive capacity for survival than FEV$_1$ alone. The two common variables included in all multidimensional prognostic indices in COPD are respiratory function – measured with postbronchodilator FEV$_1$ (%)– and dyspnea.[4,6,7,9] However the cutoffs used are COPD are respiratory function – measured with postbronchodilator FEV$_1$ values.

# FEV, Cut-Offs and Mortality in COPD Patients

## FEV, Cut-Offs and Mortality in COPD Patients

In a cohort study, we examined the relationship between FEV$_1$ values and survival in patients with COPD. Our findings indicate that FEV$_1$ values are associated with survival, with lower FEV$_1$ values being associated with a higher risk of mortality. This relationship is consistent with previous studies that have shown that FEV$_1$ values are a strong predictor of survival in COPD patients. Furthermore, our study demonstrates that FEV$_1$ values can be used to identify patients at high risk of mortality, who may benefit from targeted interventions.

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## Author Contributions

Conceived and designed the experiments: PA PMC JBS BC MM. Performed the experiments: PA PMC JBS BC MM JMM IA CC CE JJSC JPfT. Analyzed the data: PMC. Wrote the paper: PA PMC JBS BC MM JMM IA CC CE JJSC JPfT.