RESEARCH ARTICLE

Prognostic Value of the Six-Second Spirometry in Patients with Chronic Obstructive Pulmonary Disease: A Cohort Study

Eva Prats1, Elena Tejero2, Paloma Pardo2, Adelaida Gavilán2, Raúl Galera3,5, José Ramón Donado1, Miguel Ángel Racionero1, Raquel Casitas3,5, Antonio Zapatero4, Francisco García-Río3,5,6 *

1 Unidad de Neumología. Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain, 2 Servicio de Urgencias. Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain, 3 Servicio de Neumología. Hospital Universitario La Paz, IdiPAZ, Madrid, Spain, 4 Servicio de Medicina Interna. Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid, Spain, 5 CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain, 6 Universidad Autónoma de Madrid, Madrid, Spain

Abstract

Background

The six-second spirometry has been proposed as an alternative to diagnose airflow limitation, although its prognostic value in patients with chronic obstructive pulmonary disease (COPD) remains unknown. The purpose of this study was to determine the prognostic value of the postbronchodilator forced expiratory volume in 1 second (FEV1)/forced expiratory volume in 6 seconds (FEV6) ratio and FEV6 in COPD patients.

Methods and Findings

The study population consisted of 2,614 consecutive stable patients with COPD. The patients were monitored for an average period of 4.3 years regarding mortality, hospitalizations by COPD exacerbations, diagnosis of lung cancer, and annual lung function decline. The overall rate of death was 10.7 (95%CI: 8.7–12.7) per 1000 person-years. In addition to male gender, age and comorbidity, FEV6 (hazard ratio [HR]: 0.981, 95%CI: 0.968–0.003) and FEV1/FEV6 quartiles (lowest quartile (<74% pred.): HR 3.558, 95%CI: 1.752–7.224; and second quartile (74–84% pred.): HR 2.599, 95%CI: 1.215–5.561; versus best quartile (>0.89% pred.)) were independently associated with mortality, whereas FEV1 was not retained in the model. 809 patients (30.9%) had at least one hospital admission due to COPD exacerbation. In addition to sex, age, smoking and comorbidity, FEV1 and FEV1/FEV6 quartiles were independent risk factors of hospitalization. FEV6 was the only spirometric parameter independently related with lung function annual decline, while the FEV6 and FEV1/FEV6 quartiles were independent risk factors for lung cancer.
Conclusions
In a general COPD outpatient population, airflow obstruction assessed by the $\text{FEV}_1/\text{FEV}_6$ is an independent risk factor for both death and hospitalization.

Introduction
Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide and the ninth combining the years of life lost or lived with disability [1]. Since its prevalence and mortality are still increasing, it constitutes a relevant public health problem [2]. COPD is characterized by airflow limitation and therefore spirometry remains the essential test to diagnose and assess the severity of the disease. Although several multidimensional indices have shown better survival prediction than the degree of airflow limitation degree [3,4], all indices have been constructed by adding different variables—such as dyspnoea, exercise capacity, exacerbations or age—to different categories of airflow limitation. Indeed, the new GOLD stratification of COPD severity also includes the level of daily symptoms and the history of exacerbations, along with degree of airflow limitation [2].

Although the forced expiratory volume at 1 second ($\text{FEV}_1$)/forced vital capacity ($\text{FVC}$) ratio is the gold standard to identify airway limitation, its severity is usually assessed by $\text{FEV}_1$ [2]. In fact, spirometry can require prolonged expiratory effort (which can surpass 20 seconds) to achieve a plateau on the volume-time curve and a small end-of-test volume, which indicates complete lung emptying [5]. With slow lung emptying, as especially occurs in patients with airflow limitation, FVC is sensitive to expiratory time: the longer the expiratory time, the higher the FVC and the smaller the $\text{FEV}_1/\text{FVC}$ [6].

Forced expiratory volume in 6 seconds ($\text{FEV}_6$) has been proposed as a simplified alternative to FVC [7]. $\text{FEV}_6$ measurement is more easily achieved, causes less patient discomfort and is more reproducible than FVC [8]. Indeed, the $\text{FEV}_1/\text{FEV}_6$ ratio has been found to be nearly equivalent to $\text{FEV}_1/\text{FVC}$ for the diagnosis of airflow limitation [8,9]. Moreover, a meta-analysis indicated that $\text{FEV}_1/\text{FEV}_6$ can be used as a surrogate for $\text{FEV}_1/\text{FVC}$ to quantitate airflow limitation [10].

Having accepted its diagnostic utility, it seems interesting to evaluate whether the $\text{FEV}_1/\text{FEV}_6$ ratio might have an additional prognostic value in COPD patients as a marker of the degree of airflow limitation. Some previous evidence in smokers without airflow limitation suggests that the $\text{FEV}_1/\text{FEV}_6$ ratio might be an independent predictor for annual decline in lung function [11]. Moreover, in a cohort of elderly subjects with or without airflow limitation, Sorino et al [12] reported that the $\text{FEV}_1/\text{FEV}_6$ ratio should be an independent predictor of mortality, with a value comparable to that of $\text{FEV}_1$ but with higher repeatability. More recently, in a population-based study, it has been reported that the presence of COPD defined by an $\text{FEV}_1/\text{FEV}_6$ ratio < lower limit of normal was associated with higher overall mortality [13]. Finally, as airflow limitation has been related to higher lung cancer risk [14,15], the $\text{FEV}_1/\text{FEV}_6$ ratio, as a surrogate measurement of airflow limitation, might also be a risk factor for developing lung cancer.

Therefore, the aim of the present study was to evaluate the prognostic value of the post-bronchodilator $\text{FEV}_6$ and the $\text{FEV}_1/\text{FEV}_6$ ratio as percentage of predicted (in quartiles) as alternative indicators of airflow limitation in COPD patients.
Methods

Study design

We conducted a single-centre, observational cohort study at the Fuenlabrada Hospital, Spain. This is the only community hospital for the 9th district of the Madrid Metropolitan Area, with a population of approximately 215,000 inhabitants. The ethics committee of Area 9 (Hospital Severo Ochoa-Hospital de Fuenlabrada) has approved the study protocol and procedures. Written informed consent was not given by participants for their clinical records to be used in this study, but patient records/information was anonymized and de-identified prior to analysis.

Study population

The study population consists of COPD patients who were being treated by a general practitioner or pulmonologist. All consecutive subjects aged 40 year or older who had been sent for spirometry between April 1, 2004 and December 31, 2008 were screened, and we recruited those who met the following inclusion criteria: 1) stable clinical condition, with no respiratory infection in the previous 6 weeks, 2) postbronchodilator FEV1/FVC ratio <0.7 and <lower limit of normal, and 3) diagnosis of COPD in the patient’s clinical record, corresponding with the chronic bronchitis (491.xx) or emphysema (492.xx) codes of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). To minimize the potential misclassification of acute bronchitis as COPD, we did not include unspecified bronchitis (490.xx).

Exclusion criteria were: inability to obtain acceptable and reproducible spirometric measurements according to ATS/ERS recommendations [5]; diagnosis of asthma, cystic fibrosis, interstitial lung disease, pulmonary thromboembolic disease, active tuberculosis, chest wall disease, neuromuscular disorder, or malignant tumour; or history of thoracotomy with pulmonary resection, uncontrolled or serious diseases, or other symptoms that could potentially affect the spirometry test. Participants who received antibiotics and/or steroids in the month prior to the enrolment were also excluded. A flowchart of the recruitment process is presented in Fig 1.

Sample size calculation

Sample size was estimated to compare the hospitalization rates among the postbronchodilator FEV1/FEV6 quartiles. In patients with mild-to-severe COPD, a hospitalization/year rate of 0.28 ± 0.034 has been previously described in our country [16]. Thus, to detect an inter-group difference of 0.06 hospitalizations/year using two-sided analysis with an alpha error of 0.05, a beta error of 0.20 and 22% of drop-outs, 348 patients were necessary in each subgroup. According to the distribution of FEV1/FEV6 ratio in our area, a total of at least 2,592 patients were necessary.

Procedures

Anthropometric characteristics, smoking habit and baseline therapy (inhaled short-acting or long-acting beta-agonist, short-acting or long-acting anticholinergic, oral or inhaled corticosteroid, theophylline, N-acetyl cysteine, and/or long-term home oxygen therapy) were recorded for all patients. Spirometries were performed by the same technician with a MasterScreen Body (Jaeger-Viasys, Würtzburg, Germany), following current guidelines [5]. FVC, FEV1, and FEV6 were automatically selected as the best value of three acceptable, reproducible manoeuvres [5]. After baseline evaluation, four separate doses of 100 mg of salbutamol were given by metered dose inhaler using a spacer and spirometry was repeated after 15-min delay. Both for the
Fig 1. Flow chart of the study recruitment.

Subjects aged 40 years or older referred to spirometry [2004 – 2008]

n = 10,768

Poor quality of spirometry
- BEV > 5% FVC: 431 subjects (4%)
- Expiratory time < 6 s: 538 subjects (3.8%)
- FVC diff > 0.2 l: 1,550 subjects (15%)
- FEV₁ diff > 0.2 l: 879 subjects (10%)

7,370 subjects with acceptable and reproducible spirometry

Only prebronchodilator spirometry:
1,540 subjects

5,830 subjects with postbronchodilator spirometry

Postbronchodilator FEV₁/FVC > 0.7:
2,882 subjects

2,948 subjects with postbronchodilator FEV₁/FVC < 0.7

Postbronchodilator FEV₁/FVC > LLN:
78 subjects

Other non-COPD clinical diagnosis:
247 subjects

2,623 subjects with postbronchodilator FEV₁/FVC < 0.7 and clinical diagnosis of COPD

Incomplete records or mistakes: 9 subjects

2,614 patients with COPD
baseline examination as well as the follow-up visits, we only accepted the spirometries with quality grades A or B (three ATS/ERS acceptable maneuvers and a difference less than or equal to 0.2 l between the 2 best FVC and FEV₁).

As reference values, NHANES predictive equations were used [17]. Additional variables were collected from medical records, including baseline severity of airflow limitation according to the GOLD classification for FEV₁%pred. [18]; we likewise recorded presence of diabetes, hypertension, ischemic heart disease and/or valve disease, cor pulmonale, hepatic disease, peptic ulcer disease, psychiatric disorders, rheumatic disease, any history of stroke or deep-vein thrombosis, and any other conditions needed to determine the Charlson comorbidity index.

Follow-up and outcome measurements

Patients were treated by their general practitioner or pulmonologist according to current guidelines [18], and they were checked every 3–6 months during the follow-up period until December 31, 2009. We recorded the changes in smoking habit, comorbidity, and current treatment. The interval between spirometries during the follow-up period was established by clinical indication.

The main outcomes measured were all-cause mortality and hospitalization due to COPD exacerbation. Exacerbation of COPD was defined as an increase in at least 2 out of 3 specified symptoms (breathlessness, sputum volume, sputum purulence) requiring an urgent visit to the emergency department for additional treatment, with ICD-9-CM codes 491.21 or 491.22.

Other outcome measurements of interest were hospital admission due to pneumonia (ICD-9-CM codes 480–486), diagnosis of lung cancer (M alphanumeric codes of ICD-9-CM), and annual lung function decline. Vital status and hospitalizations were ascertained by follow-up visits, emergency department or general practitioner reports, phone contacts and clinical records. A participant was considered lost to follow-up if we could not contact the patient or if he or she had moved to another place. Results were reported for patients within a minimum follow-up of 12 months in cases of lung function decline, or within 3 months for the other cases.

Statistical analysis

Values are expressed as mean ± SD or percentage. Differences between study groups were analysed using ANOVA with Bonferroni post-hoc analysis, Student t or chi-square tests. Relationships between variables were evaluated by Pearson correlation and multiple linear regression or multiple logistic regression models.

Kaplan-Meier curves and log rank tests of both mortality and hospitalizations were performed after stratifying by analysis subgroups. On multivariate Cox regression analysis, variables were included if they were independently associated with both the outcome and the exposure (p < 0.05) or if they modified the risk ratio estimate for any of the remaining covariates (> 0.5% change). Survival models were always adjusted for age, sex, pack-years, body mass index, Charlson index and current treatment. As an additional analysis, Poisson regression with overdispersion correction by Pearson were used to assess the significance of the weighted rate ratios for hospitalization.

All effects were considered significant with a p value < 0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences, v13.0 (SPSS Inc, Chicago, IL, USA) and SAS for Windows statistical software, v9.2 (SAS Institute, Inc., Carey, NC, USA).

Results

The general characteristics of the 2,614 stable COPD patients included in the study are given in Table 1. The quartile distribution of the postbronchodilator FEV₁/FEV₆ ratio (% pred.)
was < 74% pred. (quartile 1), 74–84% pred. (quartile 2), 84–89% pred. (quartile 3), and > 89% pred. (quartile 4).

Prediction of mortality

Ninety-seven of the 2,614 evaluated patients (3.7%) died during the follow-up period of 51 ± 14 months. This represents an overall death rate of 10.7 (95CI: 8.7–12.7) per 1000 person-years. S1 Table compares the characteristics of survivors and nonsurvivors. The patients who died were predominantly males, older and heavier smokers who had lower body mass index, higher comorbidity and greater lung function impairment than survivor patients. Fig 2 shows the survival curves according to the degree of airflow limitation and the quartiles of postbronchodilator FEV₁/FEV₆%pred. Time to death was shorter in patients with COPD and lower levels of both parameters.

Table 2 shows the influence on prognosis of the variables included in the univariate survival analysis. After adjusting for all relevant confounders, significant hazard ratios (HRs) were observed for the degree of airflow limitation as well as postbronchodilator FVC%pred., FEV₆% pred., and FEV₁/FEV₆ ratio (%pred.). Finally, in the stepwise multivariate Cox regression model, only male sex, age, comorbidity, postbronchodilator FEV₆%pred., and quartiles of postbronchodilator FEV₁/FEV₆%pred. were retained as independent predictors of mortality (Table 2, Fig 2C). In contrast, airflow limitation severity, assessed by postbronchodilator FEV₁%pred., was not retained in the model.

Prediction of hospitalization due to COPD exacerbations

Eight hundred nine patients (30.9%) had at least one hospital admission due to COPD exacerbation during the follow-up period. The time to first admission was shorter for males, older patients, current or former smokers, and subjects with more morbidity, as well as in patients with more severe airflow limitation (Table 3). Lower values of postbronchodilator FEV₆%pred. and FEV₁/FEV₆%pred. were also associated with a shorter time to first COPD admission during the follow-up period (Table 3). Interestingly, when all these variables were included in the stepwise Cox multiple regression model, sex, age, Charlson morbidity index, degree of airflow limitation, and quartiles of postbronchodilator FEV₁/FEV₆%pred. were retained as independent risk factors (Table 3, Fig 3).

The weighted rate ratio for hospitalization was 0.28 (95CI: 0.23–0.33) per patient-year. This rate was higher in men than in women (0.36 ± 1.60 vs. 0.08 ± 0.25, p<0.05) and also in current or former smokers than in never smokers (0.22 ± 0.78 vs. 0.45 ± 1.95 vs. 0.08 ± 0.24, respectively; p<0.001). Moreover, the rate ratio for hospitalization due to COPD exacerbation was related to male sex, BMI, pack-years, Charlson morbidity index, and spirometric variables (S2 Table). After adjusting for confounding factors (sex, age, BMI, pack-years, and morbidity), differences in hospitalization rates were found between degrees of airflow limitation and quartiles of postbronchodilator FEV₁/FEV₆%pred. (Fig 4).

During the follow-up period, 220 COPD patients (8.4%) required hospitalization secondary to pneumonia, reaching a hospitalization rate ratio due to pneumonia of 0.05 per patient–year. Male sex, intensity of smoking history, comorbidity and current treatment with inhaled corticosteroids were identified as independent risk factors for hospital admission due to pneumonia. Postbronchodilator FEV₆%pred. and FEV₁/FEV₆%pred., but not airflow limitation severity assessed by postbronchodilator FEV₁%pred., were also identified as risk factors of pneumonia in our patients (S3 Table).
Other outcomes

Lung function decline was evaluated in 1,713 patients with a mean interval between spirometries of 3 ± 1 year (range: 1–6). The mean loss of postbronchodilator FEV1 was 48 ml/year. A direct relationship was found between annual FEV1 decline and all spirometric parameters, including postbronchodilator FEV1%pred. (r = 0.312, p = 0.0002) and FEV1/FEV6%pred.

Table 1. General characteristics of the study subjects*

|                          | Mild COPD patients | Moderate COPD patients | Severe COPD patients | Very severe COPD patients | Total COPD patients |
|--------------------------|--------------------|------------------------|----------------------|---------------------------|---------------------|
| N                        | 552                | 1448                   | 523                  | 91                        | 2614                |
| Males, %                 | 73.2               | 69.4                   | 71.5                 | 77.8                      | 70.9                |
| Age, yrs                 | 63 ± 13            | 63 ± 12                | 66 ± 11              | 64 ± 10                   | 64 ± 12             |
| Height, m                | 1.63 ± 0.09        | 1.63 ± 0.09            | 1.61 ± 0.09          | 1.63 ± 0.08               | 1.62 ± 0.09         |
| BMI, Kg/m²               | 28.0 ± 5.0         | 29.3 ± 5.6             | 28.6 ± 6.2           | 26.1 ± 5.6                | 28.8 ± 5.6          |
| Smoking status           |                    |                        |                      |                           |                     |
| Current smokers, %       | 37.5               | 36.0                   | 33.1                 | 32.5                      | 35.6                |
| Ex-smokers, %            | 41.0               | 43.5                   | 49.4                 | 53.8                      | 44.5                |
| Never smokers, %         | 21.5               | 20.4                   | 17.5                 | 13.8                      | 19.8                |
| Pack-years               | 39.9 ± 24.2        | 48.1 ± 27.4            | 54.5 ± 27.8          | 51.3 ± 24.0               | 47.9 ± 27.2         |
| Comorbidity              |                    |                        |                      |                           |                     |
| Ischemic heart disease, %| 6.2                | 7.1                    | 6.0                  | 6.7                       | 6.6                 |
| Congestive heart failure, %| 3.4             | 6.1                    | 12.1                 | 5.6                       | 6.7                 |
| Cerebrovascular disease, %| 4.2              | 3.6                    | 2.9                  | 2.2                       | 3.5                 |
| Diabetes, %              | 10.5               | 15.1                   | 18.6                 | 9.0                       | 14.6                |
| Charlson index           | 3.8 ± 2.2          | 3.9 ± 2.1              | 4.3 ± 2.1            | 3.8 ± 1.7                 | 3.9 ± 2.1           |
| Lung function            |                    |                        |                      |                           |                     |
| Postbronchodilator FVC, %pred. | 101 ± 11   | 79 ± 12                | 60 ± 11              | 47 ± 12                   | 78 ± 19             |
| Postbronchodilator FEV6, %pred. | 102 ± 11  | 79 ± 10                | 60 ± 9               | 46 ± 8                    | 79 ± 18             |
| Postbronchodilator FEV1, %pred. | 90 ± 9    | 65 ± 8                 | 41 ± 6               | 26 ± 4                    | 64 ± 19             |
| Postbronchodilator FEV1/FVC | 0.67 ± 0.04  | 0.63 ± 0.07            | 0.53 ± 0.10          | 0.43 ± 0.12               | 0.61 ± 0.09         |
| Postbronchodilator FEV1/FVC, %pred. | 88 ± 5   | 84 ± 8                 | 73 ± 13              | 60 ± 15                   | 81 ± 12             |
| Postbronchodilator FEV1/FEV6 | 0.70 ± 0.04 | 0.65 ± 0.07            | 0.56 ± 0.09          | 0.47 ± 0.08               | 0.64 ± 0.09         |
| Postbronchodilator FEV1/FEV6, %pred. | 88 ± 5   | 84 ± 7                 | 73 ± 11              | 60 ± 10                   | 81 ± 11             |
| Current treatment        |                    |                        |                      |                           |                     |
| SABA, %                  | 36.5               | 43.9                   | 50.1                 | 56.2                      | 44.0                |
| LABA, %                  | 37.6               | 63.4                   | 80.0                 | 80.9                      | 61.9                |
| SAMA, %                  | 4.4                | 7.3                    | 14.2                 | 9.0                       | 8.1                 |
| LAMA, %                  | 24.3               | 50.1                   | 65.5                 | 75.3                      | 48.6                |
| Theophyllines, %         | 0.9                | 2.5                    | 10.2                 | 25.8                      | 4.5                 |
| Inhaled corticosteroids, %| 39.2              | 61.9                   | 79.7                 | 82.0                      | 61.3                |
| NAC, %                   | 4.5                | 5.4                    | 8.8                  | 4.5                       | 5.9                 |
| LTOT, %                  | 2.7                | 7.1                    | 23.4                 | 37.1                      | 10.5                |

*Data are mean ± SD or percentage.

Definition of abbreviations: BMI = body mass index; FVC = forced vital capacity; FEV6 = forced expiratory volume in 6 seconds; FEV1 = forced expiratory volume in 1 second; SABA = short-acting betaadrenergic agonists; LABA = long-acting betaadrenergic agonists; SAMA = short acting muscarinic antagonist; LAMA = long acting muscarinic antagonist; NAC = N-acetylcysteine; LTOT = long-term oxygen therapy.

doi:10.1371/journal.pone.0140855.t001
In the linear regression analysis, the only spirometric variable retained in the model to predict FEV1 decline was postbronchodilator FEV6%pred. ($r^2 = 0.069, p = 0.0002$).

During the follow-up period, a new diagnosis of lung cancer was made in 145 patients (5.5%). In the multivariable logistic regression model, male sex, lower BMI, current smoking, Charlson morbidity index, and postbronchodilator FEV6%pred., and FEV1/FEV6%pred. were identified as independent risk factors (Table 4).

**Discussion**

The main finding of the present study was that postbronchodilator FEV6 and FEV1/FEV6 as percentage of predicted were independent prognostic factors in stable outpatients with COPD.

### Table 2. Risk factors for mortality in COPD patients.

| Risk Factor                        | Crude hazard ratio (95% CI) | p       | Model 1* (Adjusted hazard ratio (95% CI)) | p       | Model 2† (Adjusted hazard ratio (95% CI)) | p       |
|------------------------------------|----------------------------|---------|-----------------------------------------|---------|-----------------------------------------|---------|
| Males (vs. females)                | 13.898 (4.084–40.729)     | <0.001  | -                                       | -       | 9.056 (2.839–28.894)                    | 0.0002  |
| Age, yrs.                          | 1.067 (1.047–1.088)       | <0.001  | -                                       | -       | 1.060 (1.029–0.092)                     | 0.0001  |
| BMI, Kg/m²                         | 0.932 (0.896–0.969)       | <0.001  | -                                       | -       |                                         |         |
| Pack-years                         | 1.015 (1.008–1.022)       | <0.001  | -                                       | -       |                                         |         |
| Charlson morbidity index           | 1.272 (1.187–1.362)       | <0.001  | -                                       | -       | 1.162 (1.020–1.325)                     | 0.024   |
| Airflow limitation severity (GOLD) | <0.001                    |         |                                        |         |                                         |         |
| Mild (n = 343)                     | 1                         | -       | 1                                       |         |                                         |         |
| Moderate (n = 1433)                | 2.491 (0.762–8.148)       | 0.131   | 1.659 (0.501–5.490)                     | 0.407   |                                         |         |
| Severe (n = 690)                   | 7.267 (2.258–23.386)      | 0.001   | 3.615 (1.105–11.819)                    | 0.034   |                                         |         |
| Very severe (n = 148)              | 12.403 (3.614–42.568)     | <0.001  | 5.247 (1.506–18.276)                    | 0.009   |                                         |         |
| Postbronchodilator FVC, % pred.    | 0.968 (0.958–0.979)       | <0.001  | 0.981 (0.969–0.992)                     | 0.001   |                                         |         |
| Postbronchodilator FEV6, % pred.   | 0.553 (0.425–0.719)       | <0.001  | 0.973 (0.961–0.985)                     | <0.001  | 0.981 (0.968–0.993)                     | 0.003   |
| Postbronchodilator FEV1/FEV6, % pred. | <0.001                 |         |                                        |         |                                         |         |
| Q4 (>0.89% pred.)                  | 1                         | -       | 1                                       |         | 1                                       | -       |
| Q3 (0.82–0.89% pred.)              | 0.830 (0.334–2.063)       | 0.688   | 1.263 (0.497–3.213)                     | 0.624   | 1.285 (0.506–3.264)                     | 0.598   |
| Q2 (0.74–0.84% pred.)              | 2.164 (1.050–4.464)       | 0.037   | 2.711 (1.265–5.808)                     | 0.010   | 2.599 (1.215–5.561)                     | 0.014   |
| Q1 (< 0.74% pred.)                 | 4.408 (2.283–8.511)       | <0.001  | 3.897 (1.911–7.946)                     | <0.001  | 3.558 (1.752–7.224)                     | 0.0005  |

97 patients died during the follow-up period (3.7%)

*Adjusted for age, sex, body mass index, smoking status, Charlson morbidity index and current treatment.

†Stepwise multivariate model including age, sex, body mass index, smoking status, Charlson morbidity index, current treatment, airflow limitation severity and postbronchodilator values of VC, FEV6, and FEV1/FEV6.

Abbreviations: FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; FEV6 = forced expiratory volume in 6 seconds.
Postbronchodilator FEV1/FEV6%pred. and FEV6%pred., as well as male sex, older age and comorbidity, were the only variables independently associated with survival. Meanwhile, staging airflow limitation according to the original GOLD criteria, body mass index and pack-years did not yield any additional prognostic information. In addition to male sex, older age, comorbidity and FEV1%pred., FEV1/FEV6%pred. was also identified as an independent risk factor for hospitalization due to COPD exacerbation. Finally, FEV6%pred. was related to lung function decline, while FEV1/FEV6%pred. and FEV6%pred. were associated with a new diagnosis of lung cancer during the follow-up period.

The most outstanding contribution of our paper is to identify postbronchodilator FEV1/FEV6%pred. as an independent predictor of survival in a large, unselected general population of COPD outpatients. Several parameters were not independently associated with survival in the current study. Although FEV1 was higher among survivors, this difference was significant only in the univariate analysis. Several previous studies have also had findings similar to ours since they failed to find an association between FEV1 and survival in COPD [19,20].

Without a doubt, the first spirometric parameter that demonstrated prognostic capability was vital capacity, and several circumstances justify its validity in COPD patients. In addition to the severity of airflow obstruction represented by FEV1, in these patients it is important to consider the consequences of air trapping and lung parenchymal destruction, for which FVC could be an indirect indicator. In fact, in COPD patients, FVC reduction has been described in association with small airway collapse and air trapping [21]. Furthermore, the importance of

---

**Table 3. Risk factors for a first hospitalization due to COPD exacerbation.**

| Risk factor                          | Crude hazard ratio (95% CI) | p     | Multivariate stepwise Cox regression |
|--------------------------------------|-----------------------------|-------|--------------------------------------|
|                                      |                             |       | Adjusted hazard ratio* (95% CI)      | p        |
| Males (vs. females)                  | 3.232 (2.363–4.420)         | <0.001| 2.588 (1.299–3.577)                  | <0.001   |
| Age, yrs.                            | 1.037 (1.028–1.047)         | <0.001| 1.020 (1.002–1.037)                  | 0.025    |
| BMI, Kg/m²                           | 0.995 (0.977–1.014)         | 0.609 |                                      |          |
| Smoking status                       |                             |       |                                      |          |
| Never smoker (n = 474)               | 1                           | -     |                                      |          |
| Current smoker (n = 851)             | 2.598 (1.717–3.933)         | <0.001|                                      |          |
| Former smoker (n = 1064)             | 3.949 (2.659–5.867)         | <0.001|                                      |          |
| Pack-years                           | 1.013 (1.009–1.017)         | <0.001|                                      |          |
| Charlson morbidity index             | 1.192 (1.145–1.241)         | <0.001| 1.114 (1.020–1.218)                  | 0.017    |
| Airflow limitation severity (GOLD)   |                             |       |                                      |          |
| Mild (n = 487)                       | 1                           | -     |                                      |          |
| Moderate (n = 1267)                  | 4.535 (2.223–9.251)         | <0.001| 2.921 (1.175–7.258)                  | 0.021    |
| Severe (n = 451)                     | 13.346 (6.561–27.144)       | <0.001| 5.666 (2.169–14.286)                 | <0.001   |
| Very severe (n = 75)                 | 17.930 (8.440–38.089)       | <0.001| 7.288 (2.601–20.424)                 | <0.001   |
| Postbronchodilator FEV6% pred.       | 0.969 (0.963–0.975)         | <0.001|                                      |          |
| Postbronchodilator FEV1/FEV6% pred.  |                             |       |                                      |          |
| Q4 (>0.89% pred.) (n = 571)          | 1                           | -     |                                      |          |
| Q3 (82–89% pred.) (n = 570)          | 1.069 (0.712–1.606)         | 0.747 | 1.172 (0.666–2.061)                  | 0.582    |
| Q2 (74–84% pred.) (n = 570)          | 1.831 (1.274–2.632)         | 0.001 | 1.814 (1.096–3.002)                  | 0.021    |
| Q1 (< 74% pred.) (n = 570)           | 3.864 (2.778–5.374)         | <0.001| 2.107 (1.232–3.603)                  | 0.006    |

809 patients (30.9%) had at least one hospitalization due to COPD exacerbation during the follow-up period

*Adjusted for current treatment, BMI, smoking status, packs-year, postbronchodilator FEV6% pred. and all variables included in the equation.

doi:10.1371/journal.pone.0140855.t003
Comorbidities in COPD patients and their prognostic implications have been increasingly recognized over the last decade [22,23]. Several of these comorbidities, including diabetes, metabolic syndrome, heart failure, coronary disease, osteoporosis, hypertension, atrial fibrillation and muscular or hormonal disorders, affect spirometric values and are particularly related with reduced FVC [24,25]. As a surrogate parameter of FVC, it seems expectable that FEV₆ could maintain a certain prognostic capability that could be even higher than FVC in patients with airflow limitation or elderly subjects, because FEV₆ measurements are more easily achieved and more reproducible than FVC [6,10]. Although we do not have previous information in COPD patients, in elderly subjects treated at geriatric clinics for respiratory and nonrespiratory...
conditions, it has been reported that the mortality rate ratio was associated with having a low FEV6 [26].

At the same time, a decline in FVC secondary to COPD comorbidities, such as obesity, osteoporosis or heart failure, can induce a reduction in FEV1 disproportionate to the degree of airflow limitation, which would be partially compensated by the FEV1/FVC ratio. In fact, this ratio has shown advantages over FEV1 as an independent predictor for cardiovascular morbidity in patients with COPD, particularly of new episodes of ictus [27] or atrial fibrillation [25]. Also in this case, the FEV1/FEV6 ratio offers the advantage over the FEV1/FVC ratio of providing a more consistent and reproducible measurement, particularly if there is air trapping. Subjects with significant air trapping might reach and exceed their equal pressure point earlier and more peripherally before complete emptying and hence have FVC lower than expected for their age, creating a falsely high FEV1/FVC, a phenomenon that should be less likely to occur if FEV6 is used. Thus, Morris et al [28] describe that the FEV1/FEV6 ratio better identifies early anomalies in lung volumes or in diffusing capacity than FEV1/FVC, which is especially

Fig 4. Comparison of adjusted weighted rate ratio for hospitalization by degree of airflow limitation (A) and quartiles of postbronchodilator FEV1/FEV6 ratio (B). Black boxes correspond to mean adjusted for sex, age, BMI, smoking status and Charlson morbidity index. Vertical lines represent standard error of the mean.

doi:10.1371/journal.pone.0140855.g004
important since hyperinflation [29] as well as reduced diffusing capacity [30] are independent predictors of mortality in COPD.

Our data also show that the FEV1/FEV6%pred. is an independent predictor, in addition to FEV1%pred., for hospitalization due to COPD exacerbation, and is even more important in the case of hospitalizations due to pneumonia. This finding could partially agree with previous information that shows that the clinical deterioration of COPD is accompanied by a decline in the FEV1/FVC ratio at a greater magnitude than the fall in FEV1 [31]. Furthermore, in the ECLIPSE study, both FEV1 as well as the FEV1/FVC ratio were related with the development of exacerbations in the first year of follow-up [32], although the latter lost significance in the multivariate analysis. At the same time, other authors have reported that FEV1/FVC is an independent risk factor for the development of COPD exacerbation due to pneumonia [33].

As far as we know, there is no specific information about the value of the FEV1/FEV6 ratio for predicting COPD exacerbations. Nevertheless, it has a better correlation than FEV1/FVC with parameters that can contribute to exacerbation risk, such as dyspnoea, quality of life and exercise tolerance [34]. Moreover, FEV1/FEV6 predicts COPD-related structural disease on CT better than FEV1/FVC [34]. On volumetric CT scans of COPD patients, it has been observed to better correlate with the extension of structural damage (both air trapping as well as emphysematous areas), which can contribute to increase exacerbation risk while decreasing functional reserve given a respiratory infection.

Our study has several strengths and limitations. Among the former are the large number of patients included and the long follow-up period, including nearly 12,000 person–yrs. Second, the entire cohort was recruited in the same geographical area, and all clinicians followed the same COPD clinical guidelines for pharmacological and non-pharmacological treatment. Third, the follow-up information is very accurate, with few participants lost to follow-up.

### Table 4. Risk factors for a new diagnosis of lung cancer during the follow-up period*

| Risk Factor | Multivariate odds ratio (95%CI) | P       |
|-------------|---------------------------------|---------|
| Males (vs. females) | 3.748 (1.581–8.885) | 0.003   |
| BMI, Kg/m² | 0.944 (0.992–1.043) | 0.008   |
| Smoking habit | 0.131 |          |
| Never smoker (n = 474) | 1 |          |
| Current smoker (n = 851) | 2.905 (1.016–8.309) | 0.047   |
| Former smoker (n = 1064) | 2.757 (0.995–7.640) | 0.051   |
| Charlson morbidity index | 1.237 (1.105–1.3859) | 0.0002  |
| Airflow limitation severity (GOLD) | 0.281 |          |
| Mild (n = 552) | 1 |          |
| Moderate (n = 1448) | 0.608 (0.233–1.588) | 0.310   |
| Severe (n = 523) | 0.360 (0.093–1.401) | 0.141   |
| Very severe (n = 90) | 0.196 (0.034–1.139) | 0.069   |
| Postbronchodilator FEVs, % pred. | 0.976 (0.956–0.996) | 0.018   |
| Postbronchodilator FEV1/FEV6, % pred. | 0.004 |          |
| Q4 (>0.89% pred.) (n = 571) | 1 |          |
| Q3 (82–89% pred.) (n = 570) | 1.334 (0.687–2.593) | 0.395   |
| Q2 (74–84% pred.) (n = 570) | 1.354 (0.693–2.648) | 0.375   |
| Q1 (< 74% pred.) (n = 570) | 3.276 (1.587–6.762) | 0.001   |

*Multivariate logistic regression model adjusted for age and current treatment.

doi:10.1371/journal.pone.0140855.t004

During the follow-up period, a new diagnosis of lung cancer was made in 145 patients (5.5%).
Several limitations, however, need to be acknowledged. Firstly, the patients were initially diagnosed with COPD on clinical grounds using a postbronchodilator FEV₁/FVC ratio of <0.7. However, the lower limit of normal for this ratio was also employed as a selection criterion because it is considered a more reliable threshold for diagnosing airflow obstruction. Second of all, we did not discriminate between respiratory and non-respiratory mortality, nor did we consider other recognized risk factors, such as dyspnoea intensity or exacerbations, since our study was only focused on evaluating the prognostic value of different airflow limitations, which obviously should be considered together with other variables to construct multidimensional scales. Thirdly, in spite of the supposedly low diagnostic sensitivity of FEV₁/FEV₆ in patients with mild COPD [9], this variable maintains its prognostic capacity in patients with clinical confirmation of the COPD diagnosis. Lastly, all our participants were Caucasian with a clear predominance of males, reflecting the epidemiology of COPD in Spain [35]. Therefore, our results should be extrapolated to other populations with caution.

In conclusion, in a large, general COPD outpatient population, FEV₁/FEV₆%pred. (in quartiles) is an independent risk factor for both mortality as well as hospitalizations due to exacerbation. The demonstration of its prognostic value, in addition to its recognized capability to identify airflow limitation, provide this parameter with potential usefulness in both COPD diagnosis and severity classification.

Supporting Information

S1 Table. Characteristics of COPD patients according to survival. (DOC)

S2 Table. Univariate linear regression models of predictors of rate ratio for hospitalizations due to COPD exacerbation. (DOC)

S3 Table. Risk factors for hospitalization due to pneumonia during the follow-up period. (DOC)

Author Contributions

Conceived and designed the experiments: EP RG RC AZ FGR. Performed the experiments: EP ET PP AG JRD MAR. Analyzed the data: EP FGR. Contributed reagents/materials/analysis tools: EP ET PP AG JRD MAR RC RG AZ FGR. Wrote the paper: EP RC RG AZ FGR.

References

1. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380: 2197–223. doi:10.1016/S0140-6736(12)61689-4 PMID: 23245608

2. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2013; 187: 347–365. doi: 10.1164/rccm.201204-0596PP PMID: 22878278

3. Celli BR, Cote CG, Marín JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004; 350: 1005–1012. PMID: 14999112

4. García-Rio F, Soriano JB, Miravitlles M, Muñoz L, Duran-Tauleria E, Sánchez G, et al. Frequency of multi-dimensional COPD indices and relation with disease activity markers. COPD. 2013; 10: 436–443. doi:10.3109/15412555.2012.761959 PMID: 23357163
Six-Second Spirometry in COPD

1. Miller MR, Hankinson J, Brusasco V, Bugos F, Casaburi R, Coates A, et al. Standardization of spirometry. Eur Respir J. 2005; 26: 319–338. PMID: 16055882

2. Bellia V, Sorino C, Catalano F, Augugliaro G, Sicchilone N, Pistelli R, et al. Validation of FEV6 in the elderly: correlates of performance and repeatability. Thorax. 2008; 63: 60–66. PMID: 17702791

3. Ferguson GT, Enright PL, Buist AS, Higgins MW. Office spirometry for lung health assessment in adults: a consensus statement from the National Lung Health Education Program. Chest. 2000; 117: 1146–1161. PMID: 1076253

4. Swanney MP, Jensen RL, Crichton DA, Beckert LE, Cardo LA, Crapo RO. FEV6 is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. Am J Respir Crit Care Med. 2000; 162: 917–919. PMID: 10988105

5. Lamprecht B, Schimhofer L, Tiefenbacher F, Kaiser B, Buist SA, Studnicka M, et al. Six-second spirometry for detection of airway obstruction. A population-based study in Austria. Am J Respir Crit Care Med. 2007; 176: 460–464. PMID: 17556719

6. Jing JY, Huang TC, Cui W, Xu F, Shen HH. Should FEV1/FEV6 replace FEV1/FVC ratio to detect airway obstruction? A metaanalysis. Chest. 2009; 135: 991–998. doi: 10.1378/chest.08-0723 PMID: 19349398

7. Enright PL, Connett JE, Bailey WC. The FEV1/FEV6 predicts lung function decline in adult smokers. Respir Med. 2002; 96: 444–449. PMID: 12117045

8. Sorino C, Shemil D, Guerra S, Enright P, Pedone C, Augugliaro G, et al. Prognostic value of FEV1/FEV6 in elderly people. Clin Physiol Funct Imaging. 2011; 31: 101–107. doi: 10.1111/j.1475-097X.2010.00984.x PMID: 20969726

9. Menezes AMB, Pérez-Padilla R, Wehrmeister FC, Lopez-Varela MV, Muiño A, el al. FEV1 is a better predictor of mortality than FVC: the PLATINO cohort study. PlosONE. 2014; 9(10):e109732.

10. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. Ann Intern Med. 1986; 105: 503–507. PMID: 3752756

11. Fry JS, Hamling JS, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating FEV1 decline to lung cancer risk. BMC Cancer. 2012; 12: 498. doi: 10.1186/1471-2407-12-498 PMID: 23901666

12. de Marco R, Accordini S, Antò JM, Gislason T, Heinrich J, Janson C, et al. Long-term outcomes in mild/moderate chronic obstructive pulmonary disease in the European community respiratory health survey. Am J Respir Crit Care Med. 2009; 180: 956–963. doi: 10.1164/rccm.200904-0543OC PMID: 19696441

13. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999; 159: 179–187. PMID: 9872837

14. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007; 176: 532–555. PMID: 17507545

15. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest. 2003; 124: 459–467. PMID: 12907529

16. Schols AM, Slangent J, Vololivos L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998; 157: 1791–1797. PMID: 9620907

17. Brusasco V, Pellegrino A, Rodarte JR. Vital capacities in acute and chronic airway obstruction: dependence on flow and volume histories. Eur Respir J. 1997; 10: 1316–1320. PMID: 9192935

18. Clini EM, Beghè B, Fabbrì LM. Chronic obstructive pulmonary disease is just one component of the complex multimorbidities in patients with COPD. Am J Respir Crit Care Med. 2013; 187: 668–671. PMID: 23540872

19. Vanfleteren LE, Spruit MA, Groenen M, Gaffron S, van Empel VP, Bruijnzeel PL, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013; 187: 729–735. doi: 10.1164/rccm.201209-1665OC PMID: 23392440

20. Yu D, Simmons D. Association between lung capacity measurements and abnormal glucose metabolism: findings from the Crossroads study. Diabet Med. 2014; 31: 595–599. doi: 10.1111/dme.12346 PMID: 24151940

21. Johnson LS, Juhlin T, Engström G, Nilsson PM. Reduced forced expiratory volume is associated with increased incidence of atrial fibrillation: the Malmo Preventive Project. Europace. 2014; 16: 182–188. doi: 10.1093/europace/eut255 PMID: 23960091

22. Pedone C, Bellia V, Sorino C, Forastiere F, Pistelli R, Antonelli-Incalzi R. Prognostic significance of surrogate measures for forced vital capacity in an elderly population. J Am Med Dir Assoc. 2010; 11: 598–604. doi: 10.1016/j.jamda.2009.12.003 PMID: 20889097
27. Söderholm M, Zia E, Hedblad B, Engström G. Lung function as a risk factor for subarachnoid hemorrhage: a prospective cohort study. Stroke. 2012; 43: 2598–2603. PMID: 22871680

28. Morris ZQ, Huda N, Burke RR. The diagnostic importance of a reduced FEV1/FEV6. COPD. 2012; 9: 22–28. doi: 10.3109/15412555.2012.630701 PMID: 22292595

29. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005; 171: 591–597. PMID: 15591470

30. Boutou AK, Shrikrishna D, Tanner RJ, et al. Lung function indices for predicting mortality in COPD. Eur Respir J. 2013; 42: 616–625. doi: 10.1183/09031936.00146012 PMID: 23349449

31. Wouters EF, Postma DS, Fokkens B, Smith C, Kelly JL, Ward SP, et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. Thorax. 2005; 60: 480–487. PMID: 15923248

32. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010; 363: 1128–1138. doi: 10.1056/NEJMoa0909883 PMID: 20843247

33. DiSantostefano RL, Li H, Hinds D, Galkin DV, Rubin DB. Risk of pneumonia with inhaled corticosteroid/long-acting β2 agonist therapy in chronic obstructive pulmonary disease: a cluster analysis. Int J Chron Obstruct Pulmon Dis. 2014; 9: 457–468. doi: 10.2147/COPD.S60498 PMID: 24855350

34. Bhatt SP, Kim YI, Wells JM, Bailey WC, Ramsdell JW, Foreman MG, et al. FEV(1)/FEV(6) to diagnose airflow obstruction. Comparisons with computed tomography and morbidity indices. Ann Am Thorac Soc. 2014; 11: 335–341. doi: 10.1513/AnnalsATS.201308-251OC PMID: 24450777

35. Miravitlles M, Soriano JB, García-Rio F, Muñoz L, Duran-Tauleria E, Sanchez G, et al. Prevalence of COPD in Spain: Impact of undiagnosed COPD on quality of life and daily life activities. Thorax. 2009; 64: 863–868. doi: 10.1136/thx.2009.115725 PMID: 19553233