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Static lung hyperinflation is an independent risk factor for lung cancer in patients with chronic obstructive pulmonary disease

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ABSTRACT

Introduction: Static hyperinflation, a hallmark characteristic of some patients with chronic obstructive pulmonary disease, is related to higher mortality and cardiovascular morbidity. However, information about its association with lung cancer is scarce. Our aim was to evaluate whether static hyperinflation is associated with future risk of lung cancer in COPD patients.

Methods: A cohort of 848 COPD patients recruited outside the hospital setting was monitored for an average period of 4.3 years, totaling 2858 person-years, regarding diagnosis of cancer of any origin or lung cancer. Static hyperinflation was defined by functional residual capacity measured by plethysmography greater than 120% of the predicted value.

Results: The incidence rates for cancer of any origin and lung cancer were 16.0 (95%CI, 15.1–17.8) and 8.7 (95%CI, 7.7–9.8) per 1000 patient-years, respectively. Among the patients with lung cancer, non-small cell lung cancer predominated (88%). In a stepwise multivariate Cox regression model, body mass index (BMI), pack-years, Charlson index, and postbronchodilator FEV_1/FVC ratio were retained as independent predictors of cancer of any origin. In contrast, features associated with a future risk of lung cancer included older age, low BMI, increased pack-years and presence of static hyperinflation (adjusted hazard ratio: 4.617, 95%CI: 1.007–21.172, p = 0.049).

Conclusion: In a general COPD outpatient population, static hyperinflation is an independent risk factor for the development of lung cancer, which might contribute towards justifying the excess mortality identified in COPD patients with hyperinflation.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory condition characterized by airflow limitation; it is associated with high morbidity and mortality rates. COPD represents a major health problem worldwide that affects about 328 million people. It is the fourth leading cause of death, accounting for 4 million deaths every year [1–4], mainly due to cardiovascular diseases or cancer [5].

While the relationship between COPD and cancer of any origin has been less studied, the association between COPD and lung cancer has been classically attributed to tobacco consumption, a common etiological agent. However, in recent years, it has been extensively demonstrated that COPD could increase the risk of lung cancer when controlled for smoking history [6–11], suggesting the contribution of other factors, such as genetic or epigenetic alterations [12], inflammation, oxidative stress or noxious substances [10]. Due to the growing demand of lung cancer screening programs by COPD patients and as a means to improve their cost-effectiveness, it is important to have better knowledge of risk factors that are clinically identifiable in order to improve patient selection. Among these factors, the severity of airflow limitation

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; COPDGene, Genetic Epidemiology of COPD; FEV1, forced expiratory volume at 1s; FRC, functional residual capacity; FVC, forced vital capacity; GLI, Global Lung Function Initiative; NLST-ACRIN, National Lung Screening Trial-American College of Radiology Imaging Network; NSCLC, non-small cell lung cancer; PLuSS, Pittsburg Lung Cancer Screening Study; RV, residual volume; SCLC, small cell lung cancer

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has been extensively related with lung cancer incidence [8,13–17]; the same is true for the presence of emphysema [11,17–22] or the number of COPD exacerbations [14].

Due to reduced elastic-recoil pressure of the lungs combined with expiratory flow limitation [23], lung hyperinflation plays a central role in the pathophysiology of many clinical consequences of COPD. In fact, lung hyperinflation is a common functional disorder in these patients [24], which is closely related to dyspnea degree and exercise tolerance [25,26] as well as daily physical inactivity [27]. Moreover, in COPD patients, lung hyperinflation at rest (static hyperinflation), conventionally determined by a functional residual capacity (FRC) > 120% of predicted [28], is related to cardiovascular comorbidity [29,30] and is also an independent predictor of respiratory and all-causes mortality [31].

Nonetheless, although one could speculate that the mechanical stretching of the airway epithelial cells induced by lung hyperinflation together with the increase of airway inflammation and oxidative stress, previously reported in patients with hyperinflation [32], might favor the development of neoplastic transformations in the airways of these patients, no information is available about the association between static lung hyperinflation and the development of lung cancer in COPD patients. The objective of the present study was to evaluate whether static hyperinflation is an independent risk factor for the development of lung cancer or cancer of any origin in a clinical cohort of COPD patients.

2. Material and methods

2.1. Study design and patients

Between April 2004 and December 2008, a total of 848 outpatients with COPD were recruited from the Fuenlabrada cohort study. Details are available elsewhere [33,34]. Briefly, the study included all subjects aged 40 or older with airflow limitation and a clinical diagnosis of COPD treated by general practitioners or pulmonologists in the ninth district of the Madrid Metropolitan Area, Spain.

The diagnosis of COPD was based on the presence of a post-bronchodilator FEV_1/FVC ratio less than 0.7 and under the lower limit of normal with clinical confirmation in the patient's medical files (codes 491.xx or 492.xx of the International Classification of Diseases, Ninth Revision, Clinical Modification).

Exclusion criteria were: inability to obtain acceptable and reproducible spirometric and plethysmographic measurements in accordance with ATS/ERS recommendations [35,36]; previous diagnosis of asthma, cystic fibrosis, interstitial lung disease, pulmonary thromboembolic disease, active tuberculosis, chest wall disease, neuromuscular disorder, or malignant tumor; or history of thoracotomy with pulmonary resection. All included patients were required to be in stable clinical condition, with no respiratory infection in the previous 6 weeks. Participants who received antibiotics and/or steroids in the month prior to enrollment were also excluded. The study was approved by the local ethics committee (Comité Ético de Investigación Hospital Universitario de Fuenlabrada. APR-17/55).

2.2. Procedures

Anthropometric characteristics, smoking habit, current treatment, moderate-severe COPD exacerbations during last year and comorbidities were recorded for all patients. During a baseline clinical examination, spirometry and plethysmography were performed with a MasterScreen Body (Jaeger-Viasys, Würtzburg, Germany), following current guidelines [35,36]. FVC and FEV_1 were automatically selected as the best values from three acceptable, reproducible maneuvers [35]. 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 a 15-min delay. Thoracic gas volume at the level of functional residual capacity (FRC) was measured while the subjects made gentle breathing movements against the shutter at a rate of < 1 s^{-1}. A series of 3–5 technically satisfactory panting maneuvers were recorded; afterwards, the shutter was opened and subjects performed an expiratory reserve volume maneuver followed by a vital capacity maneuver. Corrections for not occluding the airway at a representative end-expiratory lung volume were made to obtain FRC [37]. FRC was reported as the mean of three or more measurements that differed less than 5 percent from the mean. Residual volume (RV) was determined by subtracting the expiratory reserve volume from the FRC. Similarly, total lung capacity (TLC) was calculated by adding the mean RV to the largest inspiratory vital capacity that was within 5% of the mean.

As reference values, Global Lung Function Initiative (GLI) and European Coal and Steel Community equations were used for spirometric parameters and static lung volumes, respectively [37,38]. Baseline severity of airflow limitation was classified according to the GOLD guidelines [39], and static lung hyperinflation was defined as FRC > 120% of predicted [28].

2.3. Follow-up and outcome measurements

Patients were treated by their general practitioner or pulmonologist following current guidelines [39], and they were checked every 3–6 months during the follow-up period until December 31, 2009. Changes in smoking habit, comorbidity and current treatment were recorded.

The primary outcome was time until a cancer diagnosis was established. The diagnosis of cancer was made by conventional clinical criteria and classified by M alphanumeric codes of ICD-9-CM, considering both the presence of lung cancer and cancer of any origin. A participant was considered lost to follow-up if we could not contact the patient or if she/he had changed residence. Results were reported for patients within a minimum follow-up of 3 months.

2.4. Statistical analysis

Continuous variables were expressed as mean ± SD or median (interquartile range), depending on their normal distribution. Categorical variables were reported as absolute numbers and percentages. Comparisons between groups were performed using the chi-squared test, Student's *t*-test or analysis of variance with Bonferroni *post hoc* analysis. Standard Cox semiparametric proportional hazard models were used to study time-to-cancer data. Kaplan-Meier curves and log rank tests of cancer-free survival were performed after stratifying by presence or not of static lung hyperinflation. In the 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 (BMI), Charlson comorbidity index, current treatment and airflow limitation severity. All effects were considered significant with a p value < 0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences, v20.0 (SPSS Inc, Chicago, IL, USA).

3. Results

A total of 848 patients with COPD were included in the analysis, totaling the experience of 2858 patient-years of follow-up time contributed to the study. Patients had a mean age ± SD of 61 ± 11 years, and 73% were males. At study entry, 39.4% of patients were current smokers and 44.8% former smokers. Based on the GOLD classification, 120 (14.1%) had mild, 443 (52.2%) had moderate, 231 (27.1%) had severe and 54 (6.6%) had very severe airflow limitation. Baseline patient characteristics according to COPD severity are presented in Table 1.

Table 1
General characteristics of the study subjects.[a]

	Total COPD patients	Mild	Moderate	Severe	Very severe	*p*-value
N	848	120	443	231	54	–
Males, %	619 (73.0)	92 (76.7)	312 (70.4)	175 (75.8)	40 (74.1)	0.358
Age, yrs.	61 ± 11	61 ± 11	63 ± 11	61 ± 10	61 ± 10	0.05
BMI, kg/m^2	28.6 ± 5.8	26.6 ± 4.1	29.5 ± 5.6	28.7 ± 6.5	25.7 ± 5.4	< 0.001
Smoking status						0.728
Current smoker, %	315 (39.4)	53 (47.3)	160 (38.6)	83 (37.6)	19 (37.3)	
Former smoker, %	358 (44.8)	43 (38.4)	189 (45.5)	103 (46.6)	23 (45.1)	
Never smoker, %	126 (15.8)	16 (14.3)	66 (15.9)	35 (15.8)	9 (17.6)	
Pack-years	47.7 ± 25.9	39.4 ± 23.5	46.8 ± 25.5	52.5 ± 27.1	52.0 ± 23.8	0.001
Moderate-severe exacerbations last year						< 0.001
None, %	558 (65.8)	98 (81.7)	313 (70.7)	119 (51.5)	28 (51.9)	
1, %	138 (16.3)	10 (8.3)	73 (16.5)	47 (20.3)	8 (14.8)	
2 or more, %	145 (17.1)	12 (10.0)	57 (12.9)	65 (28.1)	18 (33.3)	
Comorbidity						
Heart ischemic disease, %	53 (6.3)	6 (5.0)	26 (5.9)	18 (7.8)	3 (5.6)	0.713
Congestive heart failure, %	43 (5.1)	1 (0.8)	22 (5.0)	18 (7.8)	2 (3.7)	0.043
Peripheral arterial disease, %	158 (18.7)	20 (16.8)	81 (18.4)	50 (21.6)	7 (13)	0.424
Diabetes, %	116 (13.7)	6 (5.0)	69 (15.6)	37 (16.0)	4 (7.4)	0.008
Charlson comorbidity index	3.6 ± 1.9	3.4 ± 1.9	3.6 ± 2.0	3.8 ± 1.9	3.3 ± 1.5	0.161
Postbronchodilator spirometry						
FEV_1, l	1.67 ± 0.67	2.61 ± 0.56	1.81 ± 0.45	1.13 ± 0.29	0.73 ± 0.67	< 0.001
FEV_1, % pred.	59 ± 19	89 ± 8	64 ± 8	41 ± 6	26 ± 4	< 0.001
FEV_1, z-score	−2.61 ± 1.16	−7.20 ± 0.54	−2.35 ± 0.56	−3.64 ± 0.51	−4.56 ± 0.55	< 0.001
FVC, l	2.79 ± 0.96	3.90 ± 0.93	2.90 ± 0.79	2.22 ± 0.67	1.79 ± 0.69	< 0.001
FVC, %pred.	73 ± 18	103 ± 11	77 ± 11	58 ± 10	47 ± 12	< 0.001
FVC, z-score	−1.58 ± 1.30	0.30 ± .084	-1.34 ± 0.78	−2.54 ± 0-78	−3.58 ± 1.11	< 0.001
FEV_1/FVC	0.60 ± 0.10	0.67 ± 0.04	0.63 ± 0.07	0.52 ± 0.10	0.44 ± 0.13	< 0.001
FEV_1/FVC, z-score	−2.32 ± 1.08	−1.49 ± 0.60	−2.00 ± 0.80	−3.00 ± 1.03	−3.77 ± 1.15	< 0.001
Lung volumes						
TLC, l	5.81 ± 1.99	6.1 ± 3.10	5.66 ± 1.6	5.91 ± 1.73	6.07 ± 2.40	0.08
TLC, % pred.	102 ± 29	104 ± 48	100 ± 24	104 ± 25	104 ± 35	0.251
FRC, l	4.18 ± 1.42	4.16 ± 1.06	3.89 ± 1.21	4.55 ± 1.62	4.99 ± 2.10	< 0.001
FRC, % pred.	133 ± 40	130 ± 29	122 ± 35	144 ± 45	157 ± 59	< 0.001
FRC/TLC	0.70 ± 0.46	0.65 ± 0.13	0.66 ± 0.62	0.76 ± 0.10	0.82 ± 0.12	0.004
RV, l	3.06 ± 1.78	2.42 ± 2.95	2.82 ± 1.33	3.62 ± 1.47	4.08 ± 1.90	< 0.001
RV, % pred.	144 ± 76	113 ± 122	132 ± 57	166 ± 62	187 ± 82	< 0.001
RV/TLC	0.53 ± 0.34	0.43 ± 0.12	0.51 ± 0.45	0.60 ± 0.11	0.64 ± 0.16	< 0.001
Current treatment						
SABA or SAMA %	449 (53.1)	54 (45.4)	234 (53.1)	134 (58.0)	27 (50.0)	0.152
LABA or LAMA, %	239 (28.3)	34 (28.6)	142 (32.2)	51 (22.1)	12 (22.2)	0.034
LAMA and LABA, %	449 (53.1)	34 (28.6)	216 (49.0)	161 (69.7)	38 (70.4)	< 0.001
Inhaled corticosteroids, %	586 (69.3)	55 (46.2)	288 (65.3)	198 (85.7)	45 (83.3)	< 0.001
Oxygen therapy, %	96 (11.4)	1 (0.8)	28 (6.3)	49 (21.2)	18 (33.3)	< 0.001

Definition of abbreviations: BMI = body mass index; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; FRC = functional residual capacity; LABA = long-acting beta-adrenergic agonists; LAMA = long-acting muscarinic antagonist; RV = residual volume; TLC = total lung capacity.

[a] Data are mean ± SD or percentage. *p*-value by Chi-squared test of analysis of variance.

3.1. Risk of cancer of any origin

After completing the follow-up period, 47 (5.5%) patients were diagnosed with cancer of any origin. This represents an overall cancer rate of 16.0 (15.1–17.8) per 1000 patient-years. The characteristics of COPD patients who developed cancer of any origin during the follow-up period compared to those who did not are shown in Table 2.

Risk factors related to a diagnosis of cancer of any origin during the follow-up period are summarized in Table 3. In the crude model, male sex, advanced age, low BMI, and high-intensity smoking habit or Charlson morbidity index were significantly related to a diagnosis of cancer. Moreover, airflow limitation (assessed by postbronchodilator FEV_1 or FEV_1/FVC), hyperinflation (FRC) and air trapping (RV) were identified as risk factors for cancer of any origin. However, in the stepwise multivariate Cox regression model, only BMI, pack-years, Charlson index, and postbronchodilator FEV_1/FVC ratio were retained as independent predictors of cancer of any origin (Table 3).

3.2. Risk of lung cancer

25 patients (2.9%) were diagnosed with lung cancer, which represents an overall lung cancer rate of 8.7 (7.7–9.8) per 1000 patient-years. Specifically, 22 (88%) patients had non-small cell lung cancer (NSCLC) and 3 (12%) had small cell lung cancer (SCLC).

The patients who developed lung cancer were more often older men who had lower BMI, more accumulated intensity of smoking and more comorbidity. In turn, these patients had lower FEV_1 and FEV_1/FVC and higher FRC than patients with COPD who did not develop lung cancer (Table 4). In the univariate survival analysis, significant hazard ratios (HR) were observed for male sex, age, BMI, smoking history, Charlson morbidity index, postbronchodilator FEV_1 and FEV_1/FVC, and FRC (Table 5). Last of all, in the stepwise multivariate Cox regression model, age, BMI and pack-years were retained as independent predictors. Moreover, the presence of static hyperinflation, defined by an FRC greater than 120% predicted, was also identified as an independent risk factor for lung cancer (adjusted hazard ratio: 4.617, 95%CI: 1.007–21.172, p = 0.049). Fig. 1 shows the crude and adjusted Kaplan-Meier curves for free-lung cancer survival according the presence or absence of static hyperinflation, in which it is demonstrated that patients with static hyperinflation have a higher risk of developing lung cancer.

Table 2
Comparison of the baseline characteristics of COPD patients according to the development of cancer of any origin.[a]

	COPD patients without cancer	COPD patients with cancer	p
N	801	47	
Males, %	578 (72.2)	41 (87.2)	0.014
Age, yrs.	61 ± 11	66 ± 10	0.003
BMI, kg/m^2	28.8 ± 5.8	26 ± 5.0	0.002
Smoking status			0.058
Current smoker, %	298 (39.5)	17 (37.8)	
Former smoker, %	332 (44.0)	26 (57.8)	
Never smoker, %	124 (16.4)	2 (4.4)	
Pack-years	46.8 ± 25.5	59.7 ± 28.5	0.002
Charlson comorbidity index	3.6 ± 1.9	4.6 ± 1.9	< 0.001
Moderate-severe exacerbations last year			0.848
None, %	530 (95.0)	28 (5.0)	
1, %	128 (93.4)	10 (7.3)	
2 or more, %	143 (94.1)	9 (5.9)	
Lung function			
FEV_1, % pred.	59 ± 19	52 ± 19	0.011
FEV_1, z-score	−2.59 ± 1.17	−2.89 ± 1.15	0.09
FVC, % pred.	77 ± 19	76 ± 17	0.716
FVC, z-score	−1.58 ± 1.31	−1.60 ± 1.13	0.899
FEV_1/FVC	0.60 ± 0.10	0.52 ± 0.11	< 0.001
FEV_1/FVC, z-score	−2.28 ± 1.06	−2.90 ± 1–19	< 0.001
TLC, % pred.	102 ± 30	106 ± 24	0.318
FRC, % pred.	132 ± 40	149 ± 44	0.004
FRC/TLC	0.69 ± 0.47	0.77 ± 0.15	0.223
RV, % pred.	141 ± 76	163 ± 66	0.049
Static lung hyperinflation, %	476 (59.5)	38 (80.9)	0.002

Definition of abbreviations: BMI = body mass index; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; FRC = functional residual capacity; GOLD = Global Obstructive Lung Disease; RV = residual volume; TLC = total lung capacity.

[a] Data are mean ± SD or percentage. *p*-value by t-Student or Chi-squared tests.

Table 4
Comparison of the baseline characteristics of COPD patients according to the development of lung cancer.[a]

	COPD patients without lung cancer	COPD patients with lung cancer	p
N	823	25	
Males, %	595 (72.3)	24 (96)	0.004
Age, yrs.	61 ± 11	67 ± 8	0.002
BMI, kg/m^2	29 ± 6	25 ± 5	0.001
Smoking status			0.089
Current smoker, %	303 (39.1)	12 (48.0)	
Former smoker, %	345 (44.6)	13 (52.0)	
Never smoker, %	126 (16.3)	0 (0.0)	
Pack-years	47.0 ± 25.5	65.4 ± 30.5	< 0.001
Charlson comorbidity index	3.6 ± 1.9	4.9 ± 2.0	0.001
Moderate-severe exacerbations last year			0.166
None, %	545 (97.7)	13 (2.3)	
1, %	133 (97.1)	4 (2.9)	
2 or more, %	144 (94.7)	8 (5.3)	
Lung function			
FEV_1, % pred.	59 ± 19	51 ± 19	0.001
FEV_1, z-score	−2.60 ± 1.17	−2.91 ± 1.10	0.194
FVC, % pred.	77 ± 19	76 ± 17	0.893
FVC, z-score	−1.57 ± 1.30	−1.56 ± 1.11	0.951
FEV_1/FVC	0.60 ± 0.10	0.50 ± 0.10	< 0.001
FEV_1/FVC, z-score	−2.30 ± 1.08	−3.07 ± 1.04	< 0.001
TLC, % pred.	102 ± 30	109 ± 15	0.195
FRC, % pred.	132 ± 40	154 ± 29	0.008
FRC/TLC	0.69 ± 0.46	0.78 ± 0.79	0.358
RV, % pred.	142 ± 76	166 ± 47	0.107
Static lung hyperinflation, %	491 (59.7)	23 (92)	< 0.001

Definition of abbreviations: BMI = body mass index; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; FRC = functional residual capacity; GOLD = Global Obstructive Lung Disease; RV = residual volume; TLC = total lung capacity.

[a] Data are mean ± SD or percentage. *p*-value by *t*-Student or Chi-squared tests.

4. Discussion

The main result of our study is the identification of static hyperinflation as an independent risk factor for the development of lung cancer in patients with COPD; meanwhile, it is not associated with the development of cancer of any origin. Identification of risk factors for lung cancer in groups of patients with higher incidence of this neoplasm is particularly important, given that this disorder is the leading cause of

Table 3
Risk factors for cancer of any origin in COPD patients.

	Crude hazard ratio (95% CI)	*p*	Multivariate analysis[a]	
			Adjusted hazard ratio (95%CI)	*p*
Males (vs. females)	2.515 (1.064–5.943)	0.036	–	–
Age, yrs.	1.049 (1.020–1.080)	0.001	–	–
BMI, Kg/m^2	0.901 (0.850–0.955)	< 0.001	0.905 (0.847–0.967)	0.003
Pack-years	1.017 (1.007–1.028)	0.001	1.012 (1.001–1.023)	0.039
Charlson comorbidity index	1.308 (1.157–1.479)	< 0.001	1.287 (1.138–1.456)	< 0.001
Moderate-severe exacerbations last year	1.003 (0.734–1.301)	0.765		
FEV_1, % pred.	0.982 (0.966–0.998)	0.024	–	–
FEV_1, z-score	0.842 (0.653–1.087)	0.187	–	–
FVC, % pred.	0.995 (0.980–1.011)	0.556		
FVC, z-score	0.963 (0.766–1.211)	0.747		
FEV_1/FVC	0.951 (0.928–0.974)	< 0.001	0.970 (0.944–0.997)	0.031
FEV_1/FVC, z-score	0.688 (0.535–0.885)	0.004	–	–
TLC, % pred.	1.004 (0.994–1.014)	0.413		
FRC, % pred.	1.007 (1.002–1.003)	0.012	–	–
FRC > 120% pred.	2.721 (1.311–5.619)	0.007	–	–
RV, % pred.	1.003 (1.000–1.007)	0.057		

Definition of abbreviations: BMI = body mass index; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; FRC = functional residual capacity; RV = residual volume; TLC = total lung capacity.

[a] Stepwise multivariate model including age, sex, body mass index, smoking intensity (pack-years), Charlson comorbidity index, current treatment, post-bronchodilator FEV_1/FVC, airflow limitation severity and functional residual capacity.

Table 5
Risk factors for lung cancer in COPD patients.

	Crude hazard ratio (95% CI)	*p*	Multivariate analysis[a] Adjusted hazard ratio (95%CI)	*p*
Males (vs. females)	9.014 (1.219–66.636)	0.031	–	–
Age, yrs.	1.051 (1.011–1.093)	0.011	1.066 (1.023–1.112)	0.003
BMI, kg/m^2	0.866 (0.798–0.940)	0.001	0.890 (0.811–0.976)	0.013
Pack-years	1.023 (1.010–1.037)	< 0.001	1.018 (1.004–1.031)	0.010
Charlson comorbidity index	1.348 (1.150–1.580)	< 0.001	–	–
Moderate-severe exacerbations last year	1.012 (0.734–1.316)	0.217		
FEV_1, % pred.	0.978 (0.957–1.000)	0.045	–	–
FEV_1, z-score	0.821 (0.582–1.158)	0.261		
FVC, % pred.	1.000 (0.979–1.021)	0.998		
FVC, z-score	1.033 (0.759–1.405)	0.837		
FEV_1/FVC	0.935 (0.905–0.965)	< 0.001	–	–
FEV_1/FVC, z-score	0.573 (0.408–0.805)	0.001	–	–
TLC, % pred.	1.009 (0.997–1.020)	0.130		
FRC, % pred.	1.009 (1.003–1.016)	0.007	–	–
FRC > 120% pred.	7.791 (1.837–33.046)	0.005	4.617 (1.007–21.172)	0.049
RV, % pred.	1.004 (1.000–1.008)	0.068		

Definition of abbreviations: BMI = body mass index; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; FRC = functional residual capacity; GOLD = Global Obstructive Lung Disease; RV = residual volume; TLC = total lung capacity.

[a] Stepwise multivariate model including age, sex, body mass index, smoking intensity (pack-years), Charlson comorbidity index, current treatment, post-bronchodilator FEV_1/FVC, airflow limitation severity and functional residual capacity.

cancer deaths worldwide in men, and second most common in women, with an estimated 1.6 million deaths per year [40], and screening programs need to have risk predictors to improve patient selection and increase their efficiency.

The incidence rate of both cancer of any origin and lung cancer obtained in our cohort is consistent with previous studies. With respect to cancer of any origin, our incidence rate (16.0 per 1000 patient-years) is even slightly higher than that detected in another study conducted in our country with 308 outpatients with COPD who had been followed for 3 years, in which a incidence rate of 10.3 per 1000 patient-years was reported [41]. In turn, the incidence rate of lung cancer detected in our series was higher than those reported by studies including COPD patients from primary care settings or population-based cohorts, in which incidence rates ranging from 1.58 to 6.5 per 1000 patient-years have been described [41–46]. In fact, we believe that the rigorous and detailed clinical monitoring of our patients has allowed us to identify a lung cancer incidence rate of 8.7 per 1000 patient-years, which is similar to reports in high-risk patients by some lung cancer screening programs, such as the National Lung Screening Trial-American College of Radiology Imaging Network (NLST-ACRIN) cohort (7.96–8.11/1000 person-years in 6436 high-risk cigarette smokers with airflow limitation) [47] or the Pittsburg Lung Cancer Screening Study (PLuSS) (9.07/1000 patient-years in 1553 patients with airflow limitation followed for 3 years) [18], although clearly lower than that achieved in the Pamplone prospective cohort study of 2588 COPD patients followed for a median of 60 months (16.6/1000 patient-years) [48]. In addition, regarding histological types of lung cancer, 88% of lung cancers in COPD patients from our cohort were non-small cell lung cancer, coinciding with descriptions by other authors [49].

In our patients, advanced age, low BMI, elevated pack-years index, and the presence of static hyperinflation were identified as risk factors for lung cancer. The first three are concordant with large prospective studies that report age [45,46,48,50–55], pack-years [46,50–54] and low BMI [48,50] as the strongest risk variables for lung cancer in COPD patients. In contrast, some features associated with a future risk of lung cancer in other studies have not been identified in the analysis of our cohort. In a recent case-control analysis from the COPDGene cohort, respiratory exacerbations in the last year have been directly associated with an increased risk of lung cancer [17]. However, in our COPD patients, exacerbations were not related to risk of lung cancer, neither in the crude analysis nor in the multivariate analysis. Although the sample size might have been insufficient to detect a significant association, it seems more likely that this apparent discrepancy is due to the profile of patients selected in both studies. Unlike the COPDGene cohort, our patients were younger, mostly men, with less severity of airflow limitation and with fewer exacerbations in the previous 12 months (0.26 ± 0.60 in our cohort vs. 0.60 ± 1.1 in the COPDGene cohort) [17]. On the other hand, the controversy about the role of the severity

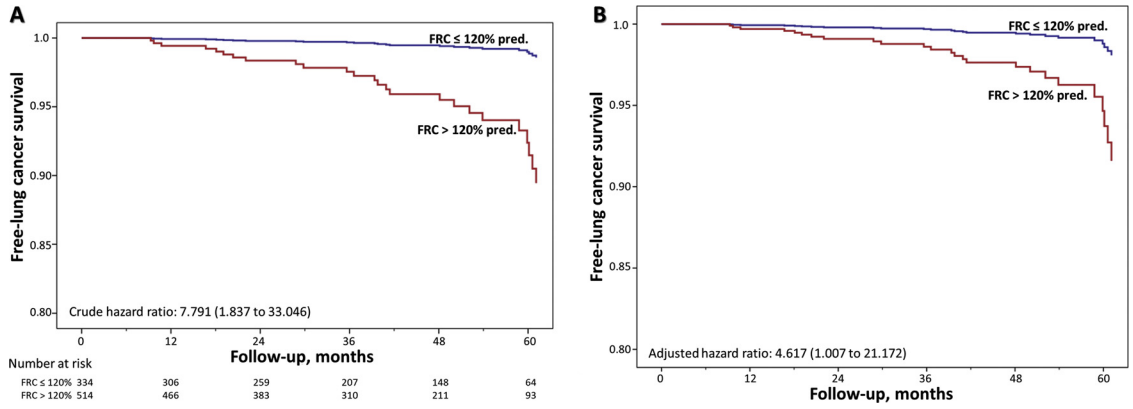

Fig. 1. Risk for lung cancer in COPD patients classified according to static lung hyperinflation. (A) Kaplan-Meier five-year crude curves. (B) Kaplan-Meier five-year curves adjusted for sex, age, BMI, packs × year, Charlson comorbidity index, current treatment and airflow limitation.

of airflow limitation as a risk factor for lung cancer also remains. While the NLST-ACRIN and PLuSS cohorts show that increasing severity of airflow limitation is directly associated with a higher risk of lung cancer [18,47], de Torres et al. [48] have reported an inverse relationship between incidence of lung cancer and FEV_1. In addition to the FEV_1, a decreased FEV_1/FVC ratio was also associated with a higher risk of lung cancer in the COPDGene study [17]. Interestingly, in our univariate analysis, the FEV_1/FVC ratio proved to be a stronger predictor of lung cancer risk than FEV_1, although it disappeared from the multivariate model when static hyperinflation was introduced.

Undoubtedly, the most striking finding of our study is that patients with static hyperinflation have a 4.6-fold increased risk for lung cancer, while their risk for cancer of any origin is not increased. Thus, it may be hypothesized that the potential effects have mainly a local impact at the airway level. Although static hyperinflation is characteristic of emphysema, whose severity assessed by computed tomography is associated with a higher incidence of lung cancer [17,50], it is important to note that this functional disorder is not exclusive of emphysema and may be present in patients with other COPD phenotypes [56].

While our data do not enable us to evaluate the mechanisms by which static hyperinflation might favor the development of lung cancer in COPD patients, there is enough previous evidence that allows us to speculate about certain possibilities. Firstly, it has been reported that stable COPD patients with hyperinflation present higher airway oxidative stress, probably due to a higher production of reactive oxygen species caused by mechanical stretching of the airway epithelial cells, a reduced free-radical scavenging capacity in the airways, or a combination of both circumstances [32]. In any case, airway oxidative stress is associated with oncogenic DNA mutation as well as cell injury, which can lead to the replication of tumor cells and the development of lung cancer in the event that cell damage is not adequately repaired [57–59]. Secondly, lung hyperinflation is related to reduced elastic recoil, loss of alveolar attachments and increased airway resistance, which can favor hypoxia through ventilation/perfusion inequalities, and hypoxia has a recognized role in the development and progression of cancer [60–63]. Finally, it is also feasible that hyperinflation and lung cancer share a genetic pathogenic pathway independent of smoking history. For example, it has been reported that a single nucleotide polymorphism in dynein axonemal heavy chain (DNAH5) could be related to hyperinflation in COPD patients [64]. In turn, other authors have described that the oncogenic driver originated by the association of DNAH5 and TRA2B genes might have a role in the development of squamous cell lung cancer [65].

Our study has several strengths and limitations. Among the former is the larger number of subjects included and the long follow-up period, including more than 2858 person-years with a broad spectrum of COPD severity. Second, because of recruitment outside a hospital setting without any specific selection, it is likely that our cohort is highly representative of the general population of patients with COPD. Third, the entire cohort was recruited in the same geographical area, and all clinicians followed the same COPD clinical guidelines for pharmacologic and non-pharmacologic management. Finally, the follow-up information is very accurate, with few participants lost to follow-up. Several limitations, however, also need to be acknowledged. Firstly, we only have computed tomography scans and lung diffusing capacity measurements for a small group of patients, since they were not routine diagnostic procedures in all COPD patients at the time of cohort generation. Therefore, our study does not reach the sample size required to assess the influence of these variables in the prediction model of lung cancer risk and more information will be required to elucidate whether lung cancer is more strongly associated with functional or morphological impairment. Secondly, all participants were white persons with a clear predominance of males, reflecting the epidemiology of COPD in Spain [66]. Therefore, our results should be extrapolated with caution to other populations. Finally, it was not possible to make an analysis of time-dependent variables to assess changes in medication and other factors. Even in the long-term, our analysis assumed that the patients' condition did not change from baseline, which may not be so for some variables.

In conclusion, this study demonstrates that static hyperinflation is an independent risk factor for the development of lung cancer in patients with COPD, which highlights the relevance of this functional alteration and could contribute to justify the higher mortality associated with hyperinflation, beyond its repercussions on the cardiovascular system.

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Conflicts of interest

The authors have no conflicts of interest in relation to the present study.

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FG-R had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. EZ, EP, ET, PP, RG, RC, EM-C, DR, AJ, and FGR contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

References

[1] K.R. Chapman, D.M. Mannino, J.B. Soriano, et al., Epidemiology and costs of chronic obstructive pulmonary disease, Eur. Respir. J. 27 (2006) 188–207.
[2] R. Lozano, M. Naghavi, K. Foreman, et al., Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet. 380 (2012) 2095–2128.
[3] GBD 2013 Mortality and Causes of Death Collaborators, Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013, Lancet. 385 (2015) 117–171.
[4] GBD 2015 Chronic Respiratory Disease Collaborators, Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet. Respir. Med. 5 (2017) 691–706.
[5] R. Rodríguez-Roisin, J.B. Soriano, Chronic obstructive pulmonary disease with lung cancer and/or cardiovascular disease, Proc. Am. Thorac. Soc. 5 (2008) 842–847.
[6] D.M. Skillrud, K.P. Offord, R.D. Miller, Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study, Ann. Intern. Med. 105 (1986) 503–507.
[7] A. Papi, G. Casoni, G. Caramori, et al., COPD increases the risk of squamous histological subtype in smokers who develop non-small cell lung carcinoma, Thorax. 59 (2004) 679–681.
[8] S. Wasswa-Kintu, W.Q. Gan, S.F. Man, P.D. Pare, D.D. Sin, Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis, Thorax 60 (2005) 570–575.
[9] R.P. Young, R.J. Hopkins, T. Christmas, P.N. Black, P. Metcalf, G.D. Gamble, COPD prevalence is increased in lung cancer, independent of age, sex and smoking history, Eur. Respir. J. 34 (2009) 380–386.
[10] A.M. Houghton, Mechanistic links between COPD and lung cancer, Nat. Rev. Cancer 13 (2013) 233–245.
[11] W. Wang, M. Xie, S. Dou, L. Cui, C. Zheng, W. Xiao, The link between chronic obstructive pulmonary disease phenotypes and histological subtypes of lung cancer: a case-control study, Int. J. Chron. Obstruct. Pulmon. Dis. 13 (2018) 1167–1175.
[12] R.P. Young, R.J. Hopkins, C.F. Whittington, B.A. Hay, M.J. Epton, G.D. Gamble, Individual and cumulative effects of GWAS susceptibility loci in lung cancer: associations after sub-phenotyping for COPD, PLoS One 6 (2011) e16476.
[13] K. Kishi, J.W. Gurney, D.R. Schroeder, P.D. Scanlon, S.J. Swensen, J.R. Jett, The correlation of emphysema or airway obstruction with the risk of lung cancer: a matched case-controlled study, Eur. Respir. J. 19 (2002) 1093–1098.
[14] J.S. Fry, J.S. Hamling, P.N. Lee, Systematic review with meta-analysis of the epidemiological evidence relating FEV1 decline to lung cancer risk, BMC Cancer 12 (2012) 498.
[15] N. Sverzellati, G. Randi, P. Spagnolo, et al., Increased mean lung density: another independent predictor of lung cancer? Eur. J. Radiol. 82 (2013) 1325–1331.
[16] R.P. Young, F. Duan, C. Chiles, et al., Airflow limitation and histology shift in the National Lung Screening Trial. The NLST-ACRIN Cohort Substudy, Am. J. Respir.

Crit. Care. Med. 192 (2015) 1060–1067.
[17] L.L. Carr, S. Jacobson, D.A. Lynch, et al., Features of COPD as predictors of lung cancer, Chest 153 (2018) 1326–1335.
[18] D.O. Wilson, J.L. Weissfeld, A. Balkan, et al., Association of radiographic emphysema and airflow obstruction with lung cancer, Am. J. Respir. Crit. Care. Med. 178 (2008) 738–744.
[19] K. Ueda, M. Jinbo, T.S. Li, T. Yagi, K. Suga, K. Hamano, Computed tomography-diagnosed emphysema, not airway obstruction, is associated with the prognostic outcome of early-stage lung cancer, Clin. Cancer. Res. 12 (2006) 6730–6736.
[20] J.P. de Torres, G. Bastarrika, J.P. Wisnivesky, et al., Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest, Chest 132 (2007) 1932–1938.
[21] Y. Li, S.J. Swensen, L.G. Karabekmez, et al., Effect of emphysema on lung cancer risk in smokers: a computed tomography-based assessment, Cancer Prev. Res. 4 (2011) 43–50.
[22] J.J. Zulueta, J.P. Wisnivesky, C.I. Henschke, et al., Emphysema scores predict death from COPD and lung cancer, Chest 141 (2012) 1216–1223.
[23] P. Gagnon, J.A. Guenette, D. Langer, et al., Pathogenesis of hyperinflation in chronic obstructive pulmonary disease, Int. J. Chron. Obstruct. Pulmon. Dis. 9 (2014) 187–201.
[24] P. Zanen, F. Rutten, A. Hoes, J. Lammers, Prevalence of hyperinflation in COPD and correlation with flow-volume indices, Chest 128 (4 Suppl) (2005) 132S–133S.
[25] D.E. O'Donnell, M. Lam, K.A. Webb, Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care. Med. 158 (1998) 1557–1565.
[26] C.B. Cooper, The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function, Am. J. Med. 119 (Suppl. 1) (2006) 21–31.
[27] F. Garcia-Rio, V. Lores, O. Mediano, et al., Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation, Am. J. Respir. Crit. Care. Med. 180 (2009) 506–512.
[28] D.E. O'Donnell, P. Laveneziana, Physiology and consequences of lung hyperinflation in COPD, Eur. Respir. Rev. 15 (2006) 61–67.
[29] C. Vassaux, L. Torre-Bouscoulet, S. Zeineldine, et al., Effects of hyperinflation on the oxygen pulse as a marker of cardiac performance in COPD, Eur. Respir. J. 32 (2008) 1275–1282.
[30] H. Watz, B. Waschki, T. Meyer, et al., Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation, Chest 138 (2010) 32–38.
[31] C. Casanova, C. Cote, J.P. de Torres, et al., Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care. Med. 171 (2005) 591–597.
[32] F. García-Rio, D. Romero, V. Lores, et al., Dynamic hyperinflation, arterial blood oxygen, and airway oxidative stress in stable patients with COPD, Chest 140 (2011) 961–969.
[33] E. Prats, E. Tejero, P. Pardo, et al., Prognostic value of the six-second spirometry in patients with chronic obstructive pulmonary disease: a cohort study, PLoS One 10 (2015) e0140855.
[34] E. Tejero, E. Prats, R. Casitas, et al., Classification of airflow limitation based on z-score underestimates mortality in patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care. Med. 196 (2017) 298–305.
[35] M.R. Miller, J. Hankinson, V. Brusasco, et al., Standardization of spirometry, Eur. Respir. J. 26 (2005) 319–338.
[36] J. Wanger, J.L. Clausen, A. Coates, et al., Standardization of the measurement of lung volumes, Eur. Respir. J. 26 (2005) 511–522.
[37] Ph.H. Quanjer, G.J. Tammeling, J.E. Cotes, O.F. Pedersen, R. Peslin, J.-C. Yernault, Lung volumes and forced ventilatory flows, Eur. Respir. J. 6 (Suppl. 16) (1993) 5–40s.
[38] Ph.H. Quanjer, S. Stanojevic, T.J. Cole, et al., Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, Eur. Respir. J. 40 (2012) 1324–1343.
[39] K.F. Rabe, S. Hurd, A. Anzueto, et al., Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary, Am. J. Respir. Crit. Care. Med. 176 (2007) 532–555.
[40] E. Brambilla, W.D. Travis, Lung cancer, in: B.W. Stewart, C.P. Wild (Eds.), World Cancer Report, World Health Organization, Lyon, 2014, pp. 350–361.
[41] J.M. Figueira Gonçalves, R. Dorta Sánchez, L.I. Pérez Méndez, et al., Incidence of cancer in outpatients with chronic obstructive pulmonary disease, Rev. Clin. Esp. 217 (2017) 387–393.
[42] V.A. Kiri, J. Soriano, G. Visick, L. Fabbri, Recent trends in lung cancer and its association with COPD: an analysis using the UK GP research database, Prim. Care Respir. J. 19 (2010) 57–61.
[43] L.P. McGarvey, M. John, J.A. Anderson, et al., Ascertainment of cause-specific mortality in COPD: operations of the TORCH clinical endpoint committee, Thorax 62 (2007) 411–415.
[44] B. Celli, M. Decramer, S. Kesten, et al., Mortality in the 4-year trial of tiotropium (UPLIFT) in patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care. Med. 180 (2009) 948–955.
[45] S.F. Liu, H.C. Kuo, M.C. Lin, et al., Inhaled corticosteroids have a protective effect against lung cancer in female patients with chronic obstructive pulmonary disease: a nationwide population-based cohort study, Oncotarget 8 (2017) 29711–29721.
[46] D.M. Mannino, S.M. Aguayo, T.L. Petty, S.C. Redd, Low lung function and incident lung cancer in the United States: data from the first National Health and Nutrition Examination Survey follow-up, Arch. Intern. Med. 163 (2003) 1475–1480.
[47] R.J. Hopkins, F. Duan, C. Chiles, et al., Reduced expiratory flow rate among heavy smokers increases lung cancer risk. Results from the National Lung Screening Trial-American College of Radiology Imaging Network Cohort, Ann. Am. Thorac. Soc. 14 (2017) 392–402.
[48] J.P. de Torres, J.M. Marin, C. Casanova, et al., Lung cancer in patients with COPD: incidence and predicting factors, Am. J. Respir. Crit. Care. Med. 184 (2011) 913–919.
[49] L.A. Hohberger, D.R. Schroeder, B.J. Bartholmai, et al., Correlation of regional emphysema and lung cancer: a lung tissue research consortium-based study, J. Thorac. Oncol. 9 (2014) 639–645.
[50] J.P. de Torres, D.O. Wilson, P. Sanchez-Salcedo, et al., Lung cancer in patients with chronic obstructive pulmonary disease. Development and validation of the COPD lung cancer screening score, Am. J. Respir. Crit. Care. Med. 191 (2015) 285–291.
[51] M.S. Tockman, N.R. Anthonisen, E.C. Wright, M.G. Donithan, Airways obstruction and the risk for lung cancer, Ann. Intern. Med. 106 (1987) 512–518.
[52] C.M. Tammemagi, P.F. Pinsky, N.E. Caporaso, et al., Lung cancer risk prediction: prostate, lung, colorectal and ovarian cancer screening trial models and validation, J. Natl. Cancer. Inst. 103 (2011) 1058–1068.
[53] M.C. Tammemagi, H.A. Katki, W.G. Hocking, et al., Selection criteria for lung-cancer screening, N. Engl. J. Med. 368 (2013) 728–736.
[54] M.C. Tammemagi, S.C. Lam, A.M. McWilliams, D.D. Sin, Incremental value of pulmonary function and sputum DNA image cytometry in lung cancer risk prediction, Cancer. Prev. Res. (Phila) 4 (2011) 552–561.
[55] M. Sandelin, S. Mindus, M. Thuresson, et al., Factors associated with lung cancer in COPD patients, Int. J. Chron. Obstruct. Pulmon. Dis. 13 (2018) 1833–1839.
[56] W. Zhang, H. Lu, L. Peng, et al., Chronic bronchitis leads to accelerated hyperinflation in COPD patients during exercise, Respirology 20 (2015) 618–625.
[57] A.M. Houghton, The paradox of tumor-associated neutrophils: fueling tumor growth with cytotoxic substances, Cell Cycle 9 (2010) 1732–1737.
[58] D. Malhotra, R. Thimmulappa, A. Navas-Acien, et al., Decline in NRF2regulated antioxidants in chronic obstructive pulmonary disease lungs due to loss of its positive regulator, DJ-1, Am. J. Respir. Crit. Care. Med. 178 (2008) 592–604.
[59] A. Singh, H. Wu, P. Zhang, C. Happel, J. Ma, S. Biswal, Expression of ABCG2 (BCRP) is regulated by Nrf2 in cancer cells that confers side population and chemoresistance phenotype, Mol. Cancer. Ther. 9 (2010) 2365–2376.
[60] G.U. Dachs, A.V. Patterson, J.D. Firth, et al., Targeting gene expression to hypoxic tumor cells, Nat. Med. 3 (1997) 515–520.
[61] J. Zhang, J. Cao, S. Ma, et al., Tumor hypoxia enhances non-small cell lung cancer metastasis by selectively promoting macrophage M2 polarization through the activation of ERK signaling, Oncotarget 5 (2014) 9664–9677.
[62] V. Kumar, D.I. Gabrilovich, Hypoxia-inducible factors in regulation of immune responses in tumour microenvironment, Immunology 143 (2014) 512–519.
[63] Q. Wang, D.F. Hu, Y. Rui, A.B. Jiang, Z.L. Liu, L.N. Huang, Prognosis value of HIF-1α expression in patients with non-small cell lung cancer, Gene 541 (2014) 69–74.
[64] J.H. Lee, M.L. McDonald, M.H. Cho, et al., DNAH5 is associated with total lung capacity in chronic obstructive pulmonary disease, Respir. Res. 15 (2014) 97.
[65] F. Li, Z. Fang, J. Zhang, et al., Identification of TRA2B-DNAH5 fusion as a novel oncogenic driver in human lung squamous cell carcinoma, Cell Res. 26 (2016) 1149–1164.
[66] M. Miravitlles, J.B. Soriano, F. Garcia-Rio, et al., Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities, Thorax 64 (2009) 863–868.