Chronic Obstructive Pulmonary Disease in Lung Cancer Patients: Prevalence, Underdiagnosis, and Clinical Characterization

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Keywords

Lung cancer · Chronic obstructive pulmonary disease · Prevalence · Underdiagnosis

Abstract

Background: Lung cancer (LC) and chronic obstructive pulmonary disease (COPD) are associated with increased morbidity and mortality. The differential clinical and functional features among LC patients with or without COPD have not been defined. **Objectives:** The aims of this study were to examine the prevalence and underdiagnosis rate of COPD in LC patients and to compare the clinical and functional features of LC patients with and without COPD. **Methods:** We designed a multicenter hospital-based study including all LC cases diagnosed from January 2014 to August 2016. We assessed epidemiological, clinical, radiological, functional, and histological variables in all cases. **Results:** We recruited 602 patients with LC, most of them men (77.9%), with a median age of 67 ± 15 years. The COPD prevalence among LC patients was 51.5%, with a underdiagnosis rate of 71.6%. The LC+COPD patients were older and the proportion of men was higher compared with the LC-only patients. The

LC+COPD patients had more pack-years, more squamous LC, a lower monoxide transfer coefficient (KCO), and higher Charlson index scores than patients with LC only. The median survival of LC-only patients was 37% longer than that of LC+COPD patients (22 vs. 16 months), but this difference was not statistically significant. **Conclusions:** Among LC patients, COPD is prevalent and underdiagnosed. Patients with LC+COPD more often have squamous LC, have greater comorbidities, and have a lower KCO. More effort should be made for an early diagnosis of COPD to select patients at higher risk of developing LC.

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Introduction

Lung cancer (LC) is the leading cause of cancer death worldwide, accounting for more than 1,400,000 annual deaths. Overall, the 5-year LC survival is poor, approximately 15%. Chronic obstructive pulmonary disease (COPD) is the fourth cause of death worldwide, with a current prevalence around 10% [1–5]. Tobacco consumption is the main risk factor for COPD and LC. Ap-

proximately 26% of heavy smokers develop clinically significant COPD. Overall, COPD affects 15–20% of smokers, while 80% of LC patients are smokers or ex-smokers. Besides tobacco use, there are other common features associated with COPD and LC, such as some genetic backgrounds, environmental exposures, and common underlying inflammatory processes. Indeed, some studies have demonstrated that COPD is a risk factor for LC development, apart from smoking [6–11].

The prevalence of COPD among LC patients is unclear, although it seems to affect at least 28–40% [12–14]. Also, the underdiagnosis of COPD is quite high in most series, including patients with LC, some studies having reported a previous diagnosis of COPD in 7.1% of LC patients [15]. Although there is a clear association between COPD and LC, the differential clinical and functional features among LC patients with or without COPD have not been defined. Some epidemiological studies of smokers showed that lower forced expiratory volume in 1 s (FEV₁) is strongly associated with an increased risk of LC, although other studies observed that the risk of LC decreases with an increase in airflow obstruction [16–18]. The prognosis of LC is worse when COPD is also present due to higher morbidity and mortality [19]. However, there is little information about the relationship between COPD severity and LC development and the influence of a previous COPD diagnosis on the staging on LC.

Pulmonary emphysema is the enlargement of airspaces distal to the terminal bronchioles, accompanied by destruction of their walls [14]. Computed tomography-detected emphysema was associated with an increased risk of LC, even for never-smokers [14, 20, 21]. The diffusing capacity for carbon monoxide (DL_{CO}) is a surrogate marker of emphysema and correlates well with computed tomography-determined emphysema; however, the degree of association between DL_{CO} and LC development is unclear. De-Torres et al. [22] developed a score that includes DL_{CO} levels, designed to help identify patients with COPD with the highest risk of developing LC. The aims of this study were to examine the prevalence and underdiagnosis of COPD in LC patients at the time of diagnosis and to compare the clinical and functional features as well as the survival of LC patients with and without COPD.

Patients and Methods

Study Design

We designed a multicenter hospital-based study consisting of a prospectively recruited cohort of all consecutive LC cases from January 2014 to August 2016 at the Vigo and Ourense University

Hospitals. Patients were followed until death or until the study end on August 31, 2016. The numbers of inhabitants covered by the third-level hospitals were 450,000 and 255,000, respectively. The Vigo pulmonary department applies practically all pulmonary techniques and procedures. It includes a Lung Cancer Rapid Diagnosis Unit as part of a multidisciplinary approach initiated by an electronic system where radiologists alert pulmonologists when there is a radiological suspicion of LC [23]. This unit assesses around 95% of all LC patients in the area. Most of the imaging studies come from primary care, emergency rooms, and preoperative consultations.

The diagnosis of LC was made after suggestive radiological findings with pathologic confirmation. The histological type was obtained by reviewing the pathology report. All patients were assigned TNM stages [24] after complete staging processes and directed to oncologic and/or surgical treatment according to the decision of a multidisciplinary committee. COPD was defined following the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations as the presence of persistent respiratory symptoms and an FEV₁/forced vital capacity ratio <0.70 after a bronchodilator test [25]. We excluded patients unwilling to participate, those with contraindications or incapable of performing spirometric tests correctly, and patients with any pulmonary obstructive disease other than COPD.

Methods

The collected data included basic demographics: age, sex, tobacco history, functional variables (comorbidity assessed by the Charlson index [26], FEV₁, DL_{CO}, and the monoxide transfer coefficient [KCO]), and body mass index (BMI). The histological type of LC was also included as well as the stage at diagnosis according to the TNM seventh edition's descriptors [24]. Other data necessary for COPD characterization were included, such as the GOLD and the Spanish Guideline for COPD (GesEPOC) classifications valid at study onset (2014) [25, 27], the COPD Assessment Test [28], or the BODE or BODEx indexes [29, 30]. We also calculated the COPD-LUCSS-DL_{CO} score [22].

Smokers were defined as participants who had smoked 100 or more cigarettes in their lifetime. Current smokers were those who had smoked more than one cigarette in the month prior to enrollment or quit within 1 year of enrollment. The remaining smokers were classified as ex-smokers. Never smokers were defined as having smoked less than 100 cigarettes in their lifetime [12]. Spirometry was performed at the LC diagnosis by a technician specialized in respiratory functional tests. It was carried out with a Masterlab pneumatic-type spirometer (Jaeger AG, Würzburg, Germany), using acceptability and reproducibility criteria from the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) [31] and the European Respiratory Society (ERS) [32] guidelines, with the 2012 multi-ethnic reference values for spirometry for the 3–95 year range [33]. A bronchodilator test was performed in all cases by administering 400 µg of salbutamol in 4 puffs (100 µg per puff) at 30-s intervals.

Analysis

We first performed a descriptive analysis of all included variables. Then we developed a univariate analysis to evaluate differences between patients with LC+COPD and LC only for the assessed variables. The Student *t* test was used for quantitative variables and the χ^2 test to compare percentages for qualitative vari-

Table 1. Univariate analysis comparing patients with LC+COPD and LC only

	LC+COPD (n = 310)	LC only (n = 292)	p value
Male sex	275 (88.7%)	194 (66.4%)	<0.0001
Age, years	69 (15)	66 (13.7)	<0.0001
Body mass index	25.6 (5.6)	27.03 (6)	0.01
Any tobacco history	304 (98.4%)	209 (73.6%)	<0.0001
Active smokers	147 (47.7%)	129 (45.6%)	ns
Pack-years	49.5 (30.5)	39.5 (30)	<0.0001
Small-cell lung cancer	42 (14%)	25 (8.7%)	0.03
Non-small-cell lung cancer	258 (86%)	264 (91.3%)	0.03
Adenocarcinoma	112 (37.7%)	182 (63.6%)	<0.0001
Squamous	110 (37%)	43 (15%)	<0.0001
Advanced stage at diagnosis ¹	157 (53.8%)	156 (54.7%)	ns
FEV ₁ at LC diagnosis, %	55.5 (28.4)	87.8 (23.6)	<0.0001
DL _{CO} at LC diagnosis, %	63 (26.7)	72.95 (24.3)	<0.0001
KCO at LC diagnosis, %	64 (38.6)	76.8 (18.8)	<0.0001
Inhaled medicines	310 (100%)	3 (7.1%)	<0.0001
Charlson index	6.9 (3.3)	5.3 (2.6)	<0.0001

Figures in parentheses are percentage or interquartile range. COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 s; KCO, monoxide transfer coefficient; LC, lung cancer; ns, not significant. ¹ Stages IIIB and IV according to the TNM 7th edition.

ables. Our limit of significance was $p < 0.05$. The same variables were entered into a multivariate logistic regression model. The Kaplan-Meier method was used to estimate the survival of all patients enrolled in the study. The analysis was performed with SPSS 21.0 (Chicago, IL, USA).

Results

We prospectively recruited 602 patients with LC (513 from Vigo and 89 from Ourense), most of them men (77.9%). The median age was 67 ± 15 years. Of the 602 patients, 52.5% were diagnosed with adenocarcinoma, 26.3% with squamous LC, 11.4% with small-cell LC (SCLC), and 9.8% with other histological types (carcinoid, sarcomatous, or undifferentiated). Concomitant COPD was diagnosed in 310 patients (51.5%), with only 28.4% of them previously diagnosed with COPD; thus, the consequent COPD underdiagnosis rate was 71.6%. Of the 28.4% with a previous diagnosis of COPD, 84.8% were diagnosed correctly (fulfilling clinical and spirometric criteria), and the other 15.2% were diagnosed according to clinical criteria only. The distribution of underdiagnosed cases did not vary according to sex (82.8% for women and 70.1% for men; $p = 0.08$). Even so, the women underdiagnosed for COPD had a reduced percentage of smokers when compared with the underdiagnosed men (93.1 vs. 99.5%, $p = 0.04$) and were diagnosed with

LC at an earlier age (63 years [IQR 16] vs. 68 years [IQR 14], $p = 0.025$).

The univariate analysis of participants according to their COPD status (LC+COPD or LC only) is presented in Table 1. The LC+COPD cases were slightly older and the proportion of men was higher compared with the LC patients. While the percentage of current smokers was similar between both groups, LC+COPD patients had a higher number of pack-years. The histological types were different among both groups, but no differences were observed for the stage at diagnosis. In the multivariate analysis (Table 2), we observed that the LC+COPD patients had significantly more squamous LC, lower KCO, and higher Charlson index scores than the patients with LC only. These results remained significant even after adjusting for FEV₁. Patients with LC+COPD tended to have higher pack-years and lower BMI; however, the differences between groups were not significant. The LC+COPD patients were GOLD I and II in 73.9% of cases, GOLD A and B in 76.9% of cases, and had no exacerbations in 90.3% of cases according to the GesEPOC Spanish classification. The BODEx index was ≥ 5 in only 7.3% of patients. The LC+COPD patients had high COPD-LUCSS-DL_{CO} risk scores in 76.1% of cases. Patients with LC and a previous diagnosis of COPD (Table 3) were older, with higher pack-years, had more severe COPD, and seemed to be more symptomatic.

Table 2. Univariate and multivariate analyses comparing patients with LC+COPD and LC only

	Univariate		Multivariate	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Male sex	0.27 (0.17–0.42)	<0.001	1.11 (0.28–4.27)	0.88
Age	1.04 (1.02–1.06)	<0.001	1.02 (0.96–1.07)	0.48
Body mass index	0.93 (0.80–0.97)	<0.001	0.88 (0.77–1.01)	0.07
Pack-years	1.02 (1.02–1.03)	<0.001	1.01 (0.99–1.04)	0.09
Squamous LC	3.17 (2.11–4.77)	<0.001	5.74 (1.71–19.29)	0.05
Advanced stage at diagnosis ¹	0.98 (0.70–1.37)	0.48	0.52 (0.17–1.62)	0.26
FEV ₁ at LC diagnosis	0.94 (0.92–0.95)	<0.01	0.92 (0.90–0.95)	<0.001
KCO at LC diagnosis	0.97 (0.96–0.98)	<0.001	0.96 (0.93–0.99)	0.01
Charlson index	1.20 (1.11–1.30)	<0.001	1.47 (1.16–1.87)	0.002

CI, confidence interval; FEV₁, forced expiratory volume in 1 s; KCO, monoxide transfer coefficient; LC, lung cancer; OR, odds ratio. ¹ Stages IIIb and IV according to the TNM 7th edition.

Table 3. Comparison between LC+COPD patients who were previous diagnosed or underdiagnosed with COPD

	Previous COPD diagnosis (<i>n</i> = 88)	Underdiagnosed (<i>n</i> = 222)	<i>p</i> value
Male sex	82 (93.2%)	192 (86.5%)	0.08
Age, years	70.9 (8.7)	68.4 (9.8)	0.03
Body mass index	26.8 (4.4)	25.7 (4.2)	0.04
Pack-years	63.2 (31.6)	53.4 (26.5)	0.01
Small-cell lung cancer	13 (14.8%)	29 (13.1%)	0.43
Adenocarcinoma	31 (35.3%)	81 (36.5%)	0.39
Squamous LC	30 (34.1%)	80 (36.5%)	0.35
Advanced stage at diagnosis ¹	40 (45.4%)	116 (52.2%)	0.26
FEV ₁ at LC diagnosis, %	53.6 (17.8)	67.7 (18.8)	<0.001
DL _{CO} at LC diagnosis, %	52.3 (18.4)	60.1 (18.5)	0.003
KCO at LC diagnosis, %	58.9 (18.2)	68.9 (19.9)	0.001
GOLD III–IV	41 (46.6%)	39 (17.6%)	<0.001
GOLD C+D	40 (45.5%)	31 (14%)	<0.001
COPD Assessment Test	11.8 (6.6)	9.7 (5.9)	0.03
BODEx index ≥5	15 (17.1%)	7 (3.1%)	<0.001
>2 exacerbations/year	18 (20.4%)	12 (5.4%)	<0.001
High-risk COPD-LUCCS-DL _{CO}	45 (51.1%)	110 (49.5%)	0.16
Charlson index	6.9 (3.1)	6.9 (3.4)	0.08
Deceased	45 (51.1%)	109 (49.1%)	0.40

Figures in parentheses are percentage or interquartile range. BODEx, body mass index, airflow obstruction, dyspnea, and exacerbations; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; KCO, monoxide transfer coefficient; LC, lung cancer. ¹ Stages IIIb and IV according to the TNM 7th edition.

The patients with COPD and advanced or local LC are compared in Table 4. Squamous LC was frequently diagnosed in the early stages of LC, whereas SCLC was diagnosed in the advanced stages. A higher percentage of patients with an advanced stage of LC were GOLD C and D and had worse COPD Assessment Test scores.

There were no significant differences between patients with LC+COPD and LC only in terms of survival (Fig. 1); however, the differences were clinically relevant, with a median survival after 3 years for patients with LC+COPD of 16 months (95% CI 13.32–18.68) versus 22 months (95% CI 15.2–28.8) for patients with LC only (long-rank

Fig. 1. Survival curves of patients with LC+COPD and LC only. LC only: median survival 22 months (95% CI 15.2–28.8); LC+COPD: median survival 16 months (95% CI 13.32–18.68); $p = 0.7$ (log-rank). COPD, chronic obstructive pulmonary disease; LC, lung cancer.

$p = 0.7$). There were no significant differences even after adjusting for significant variables in the COX regression model (age, BMI, and Charlson index scores).

Discussion

We found that COPD is a common comorbidity in LC, with 51.5% of LC patients presenting with COPD at diagnosis. Most LC+COPD patients (71.6%) had previously been diagnosed with COPD, 85% of them after fulfilling clinical and spirometric criteria (not only according to bronchial obstruction or clinical records), which limits the possible overdiagnosis of this disease. An additional important finding is that the only differences between patients with LC+COPD and LC only are that they more frequently have squamous LC, with more comorbidities and low KCO levels. This study also assessed the important issue of underdiagnosed COPD among LC patients, particularly focusing on the differences between sexes.

The prevalence of COPD in our study is consistent with some previous results, but slightly lower than others [12, 13, 34]. Even so, we found high rates of underdiagnosis (71.6%), consistent with the available data from

Table 4. Univariate analysis comparing LC+COPD patients with local or advanced stages of LC according to the TNM 7th edition

	I–IIIa (<i>n</i> = 135)	IIIb–IV (<i>n</i> = 157)	<i>p</i> value
Male sex	118 (87.4%)	140 (89.2%)	0.38
Age, years	69.3 (9.6)	68.5 (9.5)	0.46
Body mass index	26.1 (4.0)	25.8 (4.4)	0.52
Pack-years	56.2 (29.7)	55.3 (25.6)	0.80
Small-cell lung cancer	15 (9.8%)	30 (18.1%)	0.03
Adenocarcinoma	42 (31.8%)	64 (41.8%)	0.05
Squamous LC	60 (45.5%)	45 (29.4%)	0.004
FEV ₁ at LC diagnosis, %	66.8 (17.1)	62.4 (21.4)	0.06
DL _{CO} at LC diagnosis, %	60.2 (17.4)	56.5 (19.9)	0.14
KCO at LC diagnosis, %	66.2 (18.4)	65.8 (21.6)	0.89
GOLD III–IV	29 (21.6%)	45 (28.8%)	0.10
GOLD C+D	25 (18.6%)	40 (25.6%)	0.03
CAT	8.9 (4.9)	11.2 (6.7)	0.001
BODEx index ≥5	9 (6.8%)	12 (7.8%)	0.46
>2 exacerbations/year	18 (13.4%)	11 (7.1%)	0.05
High risk, COPD-LUCSS-			
DL _{CO}	74 (74%)	75 (78.1%)	0.30
Charlson index	5.1 (1.7)	8.5 (3.5)	<0.001
Deceased	40 (29.9%)	107 (68.2%)	<0.001

Figures in parentheses are percentage or interquartile range. BODEx, body mass index, airflow obstruction, dyspnea, and exacerbations; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; KCO, monoxide transfer coefficient; LC, lung cancer.

other series [34–37]. This finding confirms that, despite the availability of national and international guidelines, COPD remains substantially underdiagnosed in patients with LC. Therefore, the treatment outcomes of patients with LC+COPD may be unfavorable due to a delayed diagnosis. In our series, there was a trend, although not significant, towards underdiagnosing more women without a tobacco history and at a younger age. The reason for this might be that other risk factors, in addition to direct smoking, could be contributing to the development of COPD, such as hormonal influences, passive smoking, and exposure to environmental and occupational pollutants [34–37].

Patients with LC+COPD with a COPD diagnosis at least 1 year prior to this study were more symptomatic and had a more severe degree of obstruction; however, patients with LC+COPD with a recent diagnosis of COPD had more exacerbations. Patients with an advanced stage of LC had a lower FEV₁ at diagnosis. It is not clear wheth-

er the presence of LC may alter lung function at the time of diagnosis. Young et al. [11] compared lung function before and after the diagnosis of LC and found only a nonsignificant small reduction in lung function of 123 mL (3%). Nevertheless, it is undeniable that LC impacts COPD evolution and prognosis and may increase disease and symptom perception in patients with a low quality of life due to cancer. In our series, squamous LC was more frequently diagnosed in the early stages, whereas SCLC was diagnosed in advanced stages, which is consistent with previous reports [19, 38, 39].

Almost all (98.4%) LC+COPD patients had a tobacco history, whereas 74% of LC-only patients did. Also, LC+COPD patients had higher pack-years; however, the difference between the groups was not significant in the multivariate analysis. This is in line with the results of other series, with tobacco exposures for both groups around 80–90%, without any significant differences in pack-years in most studies [14, 17, 20, 40]. It is possible that when it comes to heavy smokers with a high amounts of pack-years, additional tobacco exposure may make little difference. The 26% prevalence of never smokers in LC patients might also be due to residential radon exposure, since the study area was radon-prone [41].

The most frequent histological type was adenocarcinoma, consistent with data from Europe, Asia, and the United States [42–46]. Patients with LC+COPD had significantly more squamous LC and lower KCO values than patients with LC only. Squamous LC and SCLC were more frequent in patients with LC+COPD, probably due to tobacco exposure. This study found that smoking had a significantly higher effect on the SCLC risk of COPD subjects compared with non-COPD subjects [39]. Also, COPD status was independently associated with SCLC risk when adjusted for age, sex, and smoking. Squamous LC was also more frequent in smokers than adenocarcinoma and has been associated with the presence of emphysema. Smith et al. [46] found that the risk of squamous carcinoma was significantly increased among LC patients with emphysema after adjusting for age, sex, COPD, and smoking history. We found that patients with LC+COPD had significantly lower DL_{CO} values, which can indicate the presence of emphysema and correlate with the presence of squamous LC.

Patients with LC+COPD had higher Charlson index scores than patients with LC only. Considering that the distribution of advanced LC was homogeneous between groups, the differences may be due to other comorbidities.

Both entities have been described to have frequent comorbidities and to even share some, such as cardiovascular disease or diabetes, that are more prevalent in COPD. The increase in comorbidities for patients with LC+COPD may be explained by a higher prevalence of smoking in this group and persistent chronic inflammation, with many types of immune cells causing tissue damage and remodeling [47–54].

Most patients with LC+COPD were GOLD I and II, GOLD A and B, and nonexacerbators, with consequently lower BODEx indexes. These results should remain the same if we used the new GOLD classification, due to the low prevalence of GOLD D in our series. In a screening study, the vast majority of LCs appeared in patients with early-stage COPD. This suggests that LC may appear early on in the progression of COPD. This finding is important because these are the patients who might tolerate invasive therapies with curative intent and who would benefit most from an eventual LC screening [40, 55, 56]. The COPD-LUCSS- DL_{CO} is a tool designed to help identify patients with COPD at a high risk of developing LC [21]. Seventy-six percent of our LC+COPD patients would have been assigned to a high-risk group according to this scale.

There was a trend towards a difference in survival of 6 months between patients with and without COPD, which is clinically relevant but not statistically significant. This finding was probably due to the majority of our LC patients having mild to moderate COPD and the short survival time of LC patients. Also, the median survival of LC patients without COPD was 37% longer than that of patients with COPD (22 vs. 16 months); however, this difference was not statistically significant.

The main limitation of our research was that it was a cohort study with a short follow-up time (2 years). Our study has also some advantages. To our knowledge, there are few data available about the clinical and functional characteristics of patients with LC+COPD. We included a reasonable sample size with clinically relevant phenotypes, diminishing the loss of cases. Also, the COPD diagnosis was determined using clinical and spirometric criteria for all patients, diminishing the risk of a COPD overdiagnosis. The last advantage was that we included two hospitals and that the whole Galician population has public health coverage, meaning there was no selection bias for our sample as we recruited more than 95% of all LC cases diagnosed in the referral areas during the study period.

This study provides some novel information about the characterization of patients with LC+COPD. Although

adenocarcinoma was the most frequent histological type, LC+COPD patients had more squamous LC and lower KCO values. This could suggest a relationship between squamous LC, smoking, and the presence of emphysema [46]. In addition, to our knowledge, this is the first study showing differences in comorbidities between LC patients with or without COPD. In conclusion, COPD is prevalent among LC patients and greatly underdiagnosed. Patients with LC+COPD more frequently have squamous LC, with more comorbidities and low KCO levels. Future efforts should focus on the early diagnosis and management of COPD to select patients at higher risk of developing LC.

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Statement of Ethics

The study was approved by the Ethics Committee for Clinical Research of Galicia (expedient 2013/439). Informed consent was obtained from all individual participants included in the study.

Financial Disclosure and Conflicts of Interest

The authors declare that they have no conflicts of interest.

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