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Lung cancer screening in clinical practice: identification of high-risk chronic obstructive pulmonary disease patients

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SUMMARY

OBJECTIVE: The NELSON study demonstrated a positive association between computed tomography scanning and reduced mortality associated with lung cancer. The COPD-LUCSS-DLCO is a tool designed to improve screening selection criteria of lung cancer for chronic obstructive pulmonary disease patients. The aim of this study was to examine and compare the discriminating value of both scores in a community-based cohort of chronic obstructive pulmonary disease patients.

METHODS: A retrospective study of chronic obstructive pulmonary disease patients followed in pulmonology consultation for a period of 10 years (2009–2019) was conducted. The NELSON criteria and COPD-LUCSS-DLCO score were calculated for each patient at the time of the study inclusion. The lung cancer incidence was calculated for each of the subgroups during the follow-up period.

RESULTS: A total of 103 patients were included in the study (mean age 64.7±9.2 years, 88.3% male). Applying the COPD-LUCSS-DLCO score, high-risk patients have a 5.9-fold greater risk of developing lung cancer versus the low risk. In contrast, there was no significant association between NELSON selection criteria and lung cancer incidence. The area under the curve was 0.69 for COPD-LUCSS-DLCO and 0.59 for NELSON criteria. Comparing test results showed no differences.

CONCLUSIONS: The use of the COPD-LUCSS-DLCO score in clinical practice can help to detect chronic obstructive pulmonary disease patients in greater risk of developing lung cancer with better performance than NELSON criteria. Therefore, models that include a risk biomarker strategy can improve selection criteria and consequently can enhance a better lung cancer prediction.

KEYWORDS: Lung cancer. Screening. Chronic obstructive pulmonary disease.

INTRODUCTION

Lung cancer (LC) is the second most common malignancy worldwide and is responsible for the highest mortality burden[1]. The considerable majority of patients are diagnosed in advanced stages and, consequently, the overall survival at 5 years remains low[2]. Therefore, it is urgent the design of strategies to identify patients at high risk of developing LC in order to detect the disease at an early and potentially curable stage. The National Lung Screening Trial (NLST) demonstrated that screening high-risk individuals with low-dose computed tomography (LDCT) is effective in detecting early stages of the disease and achieving a reduction in LC mortality of approximately 20%[3]. More recently, the largest randomized LC screening trial in Europe, the Dutch-Belgian Randomized Lung Screening Trial (NELSON), also found reduction in LC mortality by 26% in screening with LDCT[4].

Unfortunately, we do not still have the necessary conditions in our country, Portugal, to start LC screening with LDCT and, therefore, we put our focus attention on individual patients with comorbidities and habits more associated with LC, including chronic obstructive pulmonary disease (COPD). There is plenty of evidence that establishes an association between COPD and LC[5-9]. Beyond sharing smoking as a main etiological factor, several biopathogenic pathways may explain this deadly association[10]. Additionally, several authors have suggested that the presence of emphysema increases 2- to 3-fold the risk of LC, independent of tobacco history, age, sex, airway obstruction, and body mass index (BMI)[9,11,12]. Subsequently, Torres et al. developed a COPD-specific score to predict LC risk for patients with COPD (COPD-LUCSS)[13] that is determined by four parameters, namely, age, BMI, pack-years of smoking history, and the presence of emphysema in the LDCT. However, in clinical practice, most of the patients with COPD

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do not have a chest CT available and later the same authors proposed a modified version of the score, in which diffusing capacity for carbon monoxide (DLCO) is used as a surrogate marker of emphysema (COPD-LUCSS-DLCO). This system classifies patients into high-risk group with 2.4 increased risk of death by LC when compared to the second group, i.e., the low-risk group[14].

The aim of this study was to examine and compare the discriminating ability of COPD-LUCSS-DLCO and NELSON selection criteria to identify patients with the highest risk of LC in our population of COPD patients treated in pulmonology consultations.

METHODS

Study Population

An observational retrospective study was conducted on a cohort of patients diagnosed with COPD recruited from pulmonology consultations and followed over a 10-year period, between January 1, 2009 and December 31, 2019, at the Centro Hospitalar e Universitário de Coimbra (CHUC). The inclusion criteria were an age greater than 40 years and diagnosis of COPD. The exclusion criteria were the presence of chronic respiratory disease caused by something other than COPD and personal history of oncological diseases.

Clinical and Physiological Parameters Measurements

Data were retrospectively collected from the patients' medical records, including demographic information (e.g., age, sex, and cigarette smoking), pulmonary function tests, and date of diagnosis of LC. Pulmonary function tests (e.g., spirometry and diffusing capacity) were performed according to the European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines[15]. COPD was diagnosed in patients with a history of at least 10 pack-years of cigarette smoking and a post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio less than 0.70[15]. COPD patients were classified using the grades of airway limitation according to Global Initiative for COPD (GOLD) strategy. Each patient was attributed a COPD-LUCSS-DLCO and NELSON score calculated at the time of study inclusion. The patients were subsequently divided into groups of high and low risk, according to the components of each system.

Statistical analysis

Descriptive statistics was used to describe the characteristics of all the participants. Quantitative data with a normal distribution were expressed as mean and standard deviation (SD) and those variables without normal distribution were expressed as median and interquartile range (P25–P75). Qualitative data were described using relative frequencies. The association between the COPD-LUCSS-DLCO and LC, and between the NELSON criteria and LC was assessed by Cox proportional hazards regression. To compare the predictive capacity of COPD-LUCSS-DLCO for LC based on the NELSON criteria, we performed a receiver operating analysis and intra model area under the curve (AUC) comparisons. An AUC varies between 0 and 1, in which a value of 1 indicates a perfect diagnostic tool with 100% sensitivity and 100% specificity, whereas an AUC of 0.5 implies no discrimination. All analyses were performed using the statistical program SPSS version 20.0, and all hypothesis tests were bilateral, with a significance level of 5%.

RESULTS

A total of 103 subjects were included in this retrospective cohort and their characteristics are described in Table 1. The mean age was 64.7±9.2 years, men constituted 88.3% of the patients, and 36.9% were active smokers. According to the GOLD classification, 5.8% of the patients were categorized as GOLD 1, 41.7% as GOLD 2, 43.7% as GOLD 3, and 8.7% as GOLD 4. The median follow-up time was 92.4 months (IQR 57–120). About 55.5% of the LC cases were diagnosed in the first 60 months and 61.0% in the first 72 months after inclusion.

Applying the COPD-LUCSS-DLCO, 52.4% of the individuals were qualified to the high-risk category and 47.6% to the low risk. Among the patients of the high-risk group, 15 (27.8%) of 54 individuals were diagnosed with LC during the follow-up, and 3 (6.1%) of 49 patients of the low-risk group. Using the NELSON criteria, 74.8% subjects were characterized as high risk and 25.2% subjects were characterized as low risk. In the high-risk group, 16 (20.8%) of 77 individuals developed LC, and 2 (7.7%) in 26 individuals developed LC in the low-risk group. The distribution of LC in each group is shown in Figures 1 and 2.

Furthermore, we conducted a Cox regression analysis and identified that COPD-LUCSS-DLCO scores were significantly associated with LC in our population. Hazard ratio (HR) for the high risk versus the low risk in

Table 1. Characteristics of patients with chronic obstructive pulmonary disease.

Variable	n=103
Age, mean±SD	64.7±9.2
Gender, n (%)	
Female	91 (88.3)
Male	12 (11.7)
BMI, mean±SD	26.6±5.5
Active smokers, n (%)	38 (36.9)
Former smokers, n (%)	65 (63.1)
Pack-years, mean±SD	50.9±29.5
FEV_1, %	51.4±18.0
FVC, %	84.3±19.7
DLCO, %	66.2±19.6
GOLD 2009 I/II/III/IV degrees, n (%)	5.8/41.7/43.7/8.7
COPD-LUCSS-DLCO score, n (%)	
Patients with high-risk score	54 (52.4)
Patients with low-risk score	49 (47.6)
NELSON criteria, n (%)	
Patients with high-risk score	77 (74.8)
Patients with low-risk score	26 (25.2)
Median follow-up time, months (IQR)	92 (57–120)
Lung cancer diagnoses in all patients	18
COPD-LUCSS high-risk score	15
COPD-LUCSS low-risk score	3
NELSON high-risk score	16
NELSON low-risk score	2

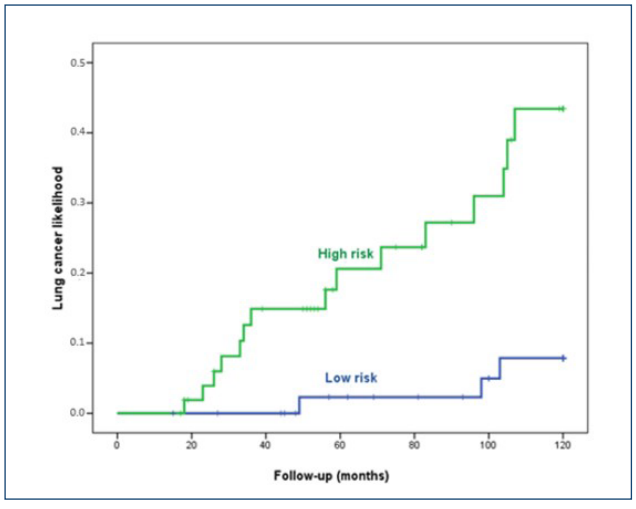

Figure 1. Incidence curves for lung cancer according to the COPD-LUCSS-DLCO score.

the COPD-LUCSS-DLCO was 5.9 (95%CI 1.71–20.44; p=0.005), showing that patients in the highest risk category have a 5.9-fold greater risk of developing LC. In contrast, there was no significant association between NELSON selection criteria and LC incidence (HR=2.8, 95%CI 0.67–12.25; p=0.168).

Concerning discriminative capacity of the two screening systems, a receiver operating characteristic analysis showed AUC values of 0.69 for the COPD-LUCSS and 0.59 for the NELSON criteria (Figure 3). However, there was no significant difference between the AUC values of two screening systems (p=0.16).

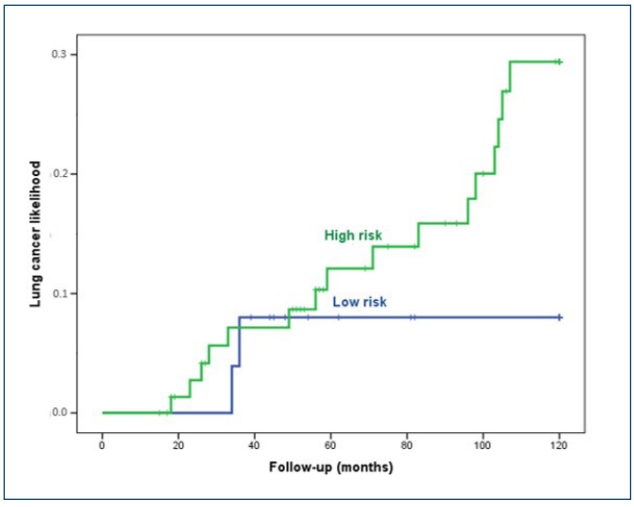

Figure 2. Incidence curves for lung cancer according to the NELSON criteria.

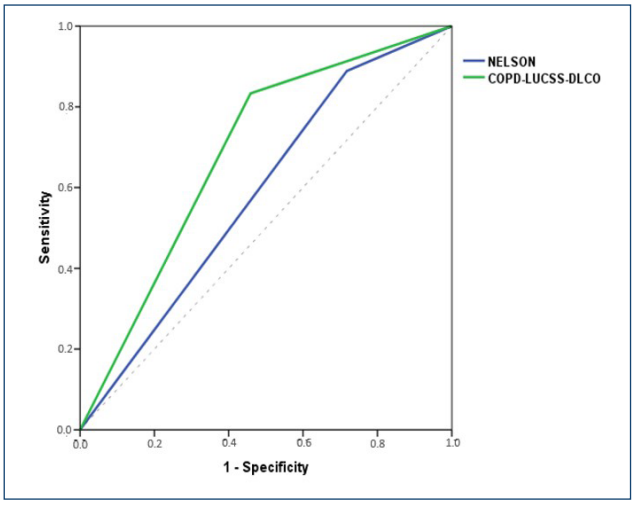

Figure 3. ROC curve of the COPD-LUCSS-DLCO and the NELSON criteria in patients with COPD.

DISCUSSION

In this study, we aimed to analyze the usefulness of COPD-LUCSS-DLCO and NELSON selection criteria to identify individuals with COPD with high risk of LC.

Our findings demonstrated that COPD-LUCSS-DLCO was significantly associated with LC and that the COPD patients in the highest risk category had a 5.9-fold greater risk of developing LC compared with the low-risk group. In opposition, the NELSON criteria indicated an incidence of LC in the high-risk patients of 2-fold than the low-risk patients, but this increase was not statistically significant.

We evaluated the discrimination capacity of the two screening systems, and we verified that both systems were identical (no statistical difference). However, COPD-LUCSS-DLCO presented a higher AUC value, approaching to the levels of acceptable discrimination (0.69). The enhanced accuracy of COPD-LUCSS-DLCO can be explained by the increased number of variables included, namely, BMI and DLCO (surrogate of emphysema). Although age and smoking criteria remain the most common metrics used to identify those eligible for screening, risk models might benefit from including other biomarkers. The use of parameters like BMI, family history of LC, occupational exposure, and genetic predictors has been previously described in the context of optimizing the selection of candidates for screening[16-19].

Our findings that the COPD-LUCSS-DLCO is associated with LC among COPD patients corroborated the findings stated by Torres et al.[14] who created this score. The authors reported a 2.4-fold increase mortality in high-risk patients compared with the low-risk group. However, Torres et al. followed their cohort for 5 years, and our study had a follow-up of 10 years, which can explain our increased mortality rate in high-risk patients. It is more likely to have LC diagnoses as the time increases.

Besides supporting previous published results, our study validates the COPD-LUCSS-DLCO use in a cohort of COPD patients recruited from pulmonology consultations. These results emphasized the utility of this score in identifying COPD patients with high risk of LC in a typical situation of standard clinical practice where, unfortunately, not all patients undergo CT.

Although the relevant results obtained, this study has some limitations that need to be considered. First, this was a retrospective study in design and, hence, we did not perform a standard protocol with CT scans in the follow-up of patients. Second, the study population belonged to a single hospital and the sample size was limited. Third, it is possible that an information bias occurred due to obtaining the variables from the patients' medical records.

CONCLUSIONS

COPD-LUCSS-DLCO score was significantly associated with LC among COPD patients, in contrast to the NELSON selection criteria. Models that include a risk biomarker strategy can improve the identification of high-risk patients and consequently can enhance a better LC prediction.

AUTHORS' CONTRIBUTIONS

SRS: Conceptualization, Formal Analysis, Investigation, Methodology, Writing – original draft. **JNC:** Formal Analysis, Investigation, Methodology, Writing – original draft. **CR:** Formal Analysis, Investigation, Supervision, Writing – review & editing. **AF:** Formal Analysis, Investigation, Supervision, Writing – review & editing. **FB:** Formal Analysis, Investigation, Supervision, Writing – review & editing.

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