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ORIGINAL ARTICLE

Lung Cancer Screening Criteria and Cardiopulmonary Comorbidities

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ABSTRACT

Introduction: Lung cancer screening criteria should select candidates with minimal cardiopulmonary comorbidities who are fit for curative lung cancer resection.

Methods: We retrospectively analyzed 728 patients with lung cancer for screening eligibility using the U.S. Preventive Services Task Force (USPSTF) 2013 criteria (n = 370). If ineligible for screening, they were further assessed for eligibility using the USPSTF 2021 (n = 121) and National Comprehensive Cancer Network group 2 (NCCN gp 2) (n = 155). Comparisons of cardiopulmonary comorbidities between patients selected by the different lung cancer screening criteria were performed. Excluding missing data, a similar comparison was done between USPSTF 2013 (n = 283) and PLCOm2012 (risk threshold ≥1.51%) (n = 118).

Results: Patients eligible for USPSTF 2021 and NCCN gp 2 had lower rates of airflow obstruction (forced expiratory volume in 1 s [FEV1]/forced vital capacity <0.7) compared with those in USPSTF 2013 (55.4% and 56.8% versus 70.5%). Both USPSTF 2021 and NCCN gp 2 groups had less severe airflow obstruction; only 11.6% and 12.9% of patients, respectively, had percent-predicted FEV1 less than 50% versus 20.3% in the USPSTF 2013 group. Comparing USPSTF 2013 and PLCOm2012 revealed no significant differences in age or the rate of airflow obstruction ($p = 0.06$ and $p = 0.09$ respectively). Nevertheless, rates of percent-predicted FEV1 less than 50% and diffusing capacity of the lungs for carbon monoxide less than 50% were lower in the PLCOm2012 group compared with those in the USPSTF 2013 group (22.3% versus 10.2% and 32.6% versus 20.0%), respectively.

Conclusions: The USPSTF 2021 qualifies an additional group of screening candidates who are healthier with better lung reserve, translating to better surgical candidacy but potentially more overdiagnosis. The PLCOm2012, with its better accuracy in selecting patients at risk of cancer, selects an older group with chronic obstructive pulmonary disease but with good lung reserve and potentially less overdiagnosis.

Keywords: Lung cancer screening; Pulmonary comorbidities; USPSTF 2013; USPSTF 2021; PLCOm2012

Introduction

The goal of lung cancer screening is to detect lung cancer at an early stage to allow for curative lung cancer resection. Hence, selection of a good surgical candidate is an important factor for determining the effectiveness of lung cancer screening criteria. The old U.S. Preventive

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Services Task Force (USPSTF) 2013 and the new USPSTF 2021 are fixed criteria on the basis of age and pack years smoked.[1,2] In contrast, PLCOm2012 is a predictive model risk-based criterion taking into account additional risk factors in deciding screening eligibility.[3]

The USPSTF in 2021 broadened its lung cancer screening criteria to include younger patients and lower smoking pack years (adults aged 50–80 y with 20 pack-year smoking history) whereas the USPSTF 2013 recommendation targets an older cohort of adults with higher smoking pack years (aged 55–80 y with 30 pack-year history). The USPSTF 2013 criteria are similar to the National Lung Cancer Screening Trial (NLST)/National Comprehensive Cancer Network group 1 (NCCN gp 1) and the Centers for Medicare and Medicaid Services, which differs only in the upper age limit being 74 and 77 years old, respectively, which makes it one of the mostly widely used and endorsed criteria.[4,5] The most recent USPSTF 2021 criteria allow for a younger group of patients with potentially lower cardiopulmonary comorbidity to benefit from lung cancer screening.

The PLCOm2012 model is the most studied prediction model[6] and was recommended by the NCCN in 2018 as an alternative guideline for patient enrollment into lung screening if they do not fulfill the fixed criteria.[7] It has been suggested that the PLCOm2012 is more sensitive but equally specific compared with USPFT 2013 for lung cancer detection.[3] Increasing age, smoking rate, personal history of cancer, family history of lung cancer, race, education level, and body mass index all contribute to the risk threshold for screening using the PLCOm2012 model rather than being limited to age and smoking exposure. This can potentially allow for patients with increased cancer risk but without the concurrent increased comorbidity and surgical risk. The NCCN introduced the NCCN gp 2 criteria which are also fixed criteria on the basis of the age and smoking pack-year requirements similar to USPSTF 2021 but with additional risk factor requirements similar to the variables from the PLCOm2012.[7]

The risk for cancer and the risk of surgery are a double-edged sword. The higher pack-year requirement for screening eligibility not only recognizes those with higher lung cancer risk but also results in higher rates of pulmonary and cardiac comorbidities.[8] In the NLST, the presence of chronic obstructive pulmonary disease (COPD) doubled the lung cancer incidence.[9] The risk of postoperative complication increases by 10% for every 5% decrement in lung function.[10] The severity of COPD is determined by the patients' pulmonary function test (PFT) results, especially forced expiratory volume in 1 second (FEV1) and diffusing capacity of the lungs for carbon monoxide (DLCO).

To assess candidacy for lung resection based on PFT, predicted postoperative (PPO) FEV1 and DLCO are calculated using the following formula: PPO = preoperative FEV1 × (1 – y/z) where y is the estimated number of lung segments to be removed and z is the total number of lung segments which is 19.[11] When lobectomy is performed for lung cancer, the number of segments removed will depend on which lobe is involved. There are three, two, and five segments in the right upper, middle, and lower lobe, respectively. On the left lung, there are five and four segments in the upper and lower lobe, respectively. Hence, a lung screening patient should expect to lose 10% to 26% (2–5 lobes) of their lung function if they undergo at least a lobar resection from a positive screening.

With the newly published USPSTF 2021 criteria and the more dynamic predictive model risk-based PLCOm2012, it is crucial to compare the cardiopulmonary comorbidities of patients selected by these criteria compared with the long-established USPSTF 2013. The aims of our study are to compare the USPSTF 2013 criteria to USPSTF 2021, NCCN gp 2, and PLCOm2012 predictive model risk-based criteria and to evaluate cardiopulmonary comorbidities and surgical candidacy of patients selected.

Materials and Methods

We retrospectively analyzed data from the ever-smoking participants with lung cancer recruited for the INflammation, Health, Ancestry and Lung Epidemiology (INHALE) study.[12,13] Briefly, participants from the general metropolitan Detroit area with lung cancer were enrolled at the Karmanos Cancer Institute or Henry Ford Health System (HFHS) within 12 months of diagnosis, between May 2012 and March 2018 at Karmanos Cancer Institute and between May 2012 and November 2014 at HFHS. They were 21 to 89 years of age at diagnosis and were able to complete a PFT with no prior lung cancer diagnosis or lung resection. Informed consent was obtained from all participants.

Data Collection

Interviews were conducted with patients to obtain their demographic information, past medical history (cancer, COPD, cardiovascular disease [CVD]), environmental exposures, and detailed smoking history. Patients either completed PFT on enrollment or had their PFT data abstracted from electronic medical record closest to the date of enrollment. The percent-predicted FEV1 and forced vital capacity (FVC) were calculated on the basis of sex, age, height, and race with reference values on the basis of the Third National Health and Nutrition Examination Survey. The PFT was reviewed by board-certified pulmonologists blinded to the study. Patients' cancer outcomes (stage, histology) were abstracted from either

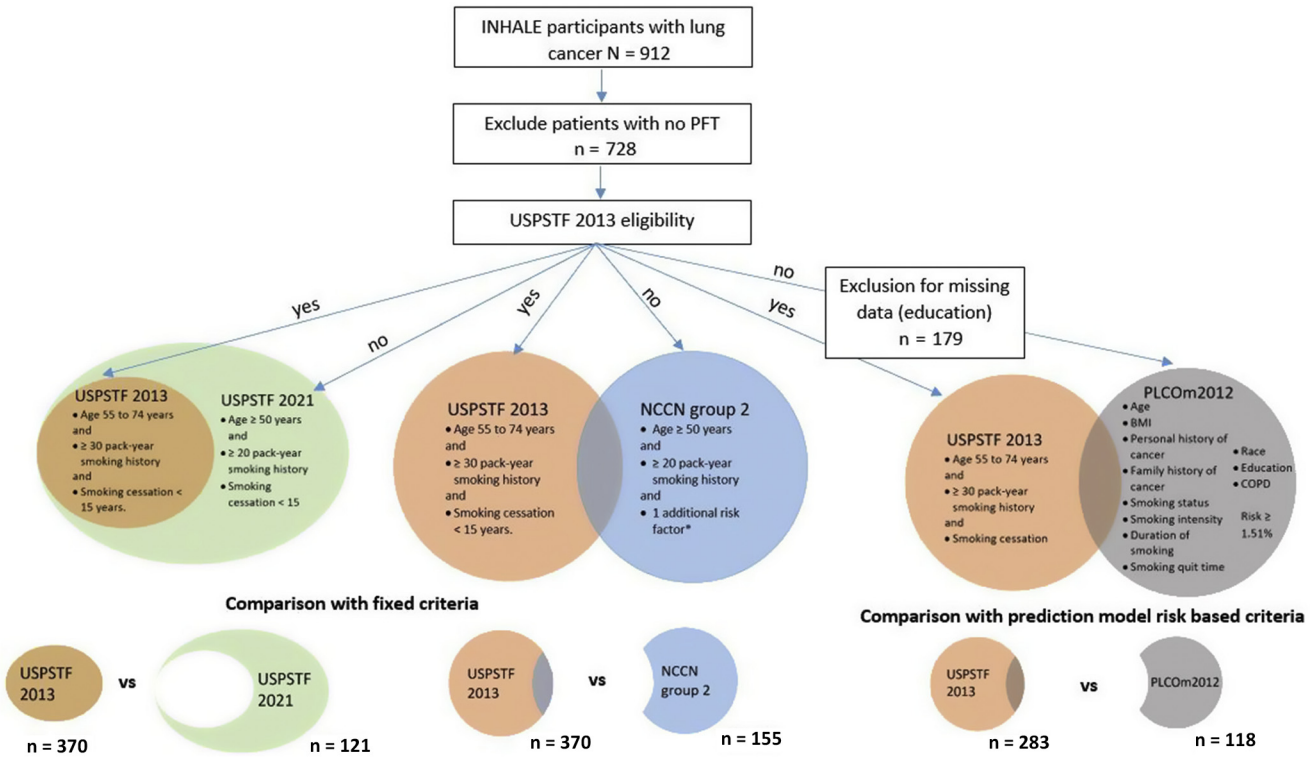

Figure 1. Patient selection for comparison between USPSTF 2013 with other fixed criteria and prediction model risk-based criteria using the INHALE patient cohort. *Additional risk factors include the following: cancer history, family history of lung cancer, radon exposure, occupational exposure (silica, cadmium, asbestos, arsenic, beryllium, chromium (VI), diesel fumes, and nickel, COPD, and pulmonary fibrosis). COPD, chronic obstructive pulmonary disease; INHALE, INflammation, Health, Ancestry and Lung Epidemiology; NCCN, NCCN gp2, National Comprehensive Cancer Network; PFT, pulmonary function test; USPSTF, U.S. Preventive Services Task Force.

the electronic medical record or the Metro Detroit Cancer Surveillance System population-based cancer registry. Institutional review board approvals were obtained from both Wayne State University and HFHS, and informed consent was obtained for all participants.

Comparison Between the Lung Cancer Screening Criteria

We assessed patients' eligibility for lung cancer screening sequentially using different eligibility criteria, starting with the USPSTF 2013 criteria as found in Figure 1. If they did not qualify, they then were assessed for eligibility using other fixed criteria under the USPSTF 2021 and the NCCN gp 2 guidelines and under the prediction model risk-based criteria of PLCOm2012 (risk threshold >1.51%/6 y) (Fig. 1). Using USPSTF 2013 as the reference, comparisons were made between patients who did not qualify for USPSTF 2013 but qualified under the fixed criteria USPSTF 2021 and NCCN gp 2. In the USPSTF 2013 comparison with the prediction model risk-based criteria, patients were excluded for missing education data needed to calculate the PLCOm2012 risk score.

Comparisons were made between patients eligible for each criterion with regard to their age, smoking pack years, PFTs, and cardiopulmonary comorbidities. History of CVD included self-reported stroke, arrhythmia, and congestive heart failure. Presence of airflow obstruction was defined as FEV1/FVC less than 0.7 per the GOLD criteria for COPD.[14] Patients' PFTs were compared with regard to presence of FEV1 less than 50%, DLCO less than 50%, and FEV1/FVC less than 0.7. History of COPD was based on patient self-report, whereas "any COPD" was based on their self-report or FEV/FVC less than 0.7.

Statistical Analysis

Continuous measures were reported as means and SDs and categorical data in frequencies and percentages. All statistical analyses were performed using either SAS version 9.4 or R version 4.1.1 with statistical significance set at p less than 0.05. Group comparisons were performed using t tests and chi-square tests as indicated.

Results

There were 728 patients with lung cancer from the INHALE cohort with PFT results who were assessed

Table 1. Description of 728 Ever-Smoker Lung Cancer Cases With PFT Data

Variables	n (%)
Age (y), mean (SD)	64.5 (9.5)
Age (y)	
<50	45 (6.2)
50-59	179 (24.6)
60-69	273 (37.5)
70-79	190 (26.1)
≥80	41 (5.7)
Sex	
Male	316 (43.4)
Female	412 (56.6)
Race	
White	455 (62.5)
African American	273 (37.5)
Pack-years, mean (SD)	46.4 (28.5)
Pack-years	
<10	34 (4.7)
10-19	81 (11.2)
20-29	104 (14.3)
≥30	507 (69.8)
Smoking status	
Former	424 (58.2)
Current	304 (41.8)
Quit time (former smokers), mean (SD)	11.5 (12.8)
Quit time (former smokers)	
<15	134 (18.4)
≥15	594 (81.6)
Comorbidities	
Cardiovascular disease[a]	188 (27.5)
COPD	293 (41.9)
Diabetes	98 (17.9)
Hypertension	394 (57.3)
% Pred FEV1%, mean (SD)	73.0 (21.8)
% Pred DLCO %, mean (SD)	62.8 (19.8)
Personal history of cancer	
No	559 (77.0)
Yes	167 (23.0)
Family history of cancer	
No	225 (30.9)
Yes	503 (69.1)
BMI	
Underweight (<18.5 kg/m^2)	30 (4.8)
Normal (18.5-24.9 kg/m^2)	233 (37.5)
Overweight (25-29.9 kg/m^2)	189 (30.4)
Obese (≥30 kg/m^2)	169 (27.2)
Missing	107
Education	
Less than 12 y	95 (17.3)
High school diploma (12 y)	222 (40.4)
More than 12 y	232 (42.3)
Missing	179
Histology	
Squamous cell carcinoma	203 (28.0)
Small cell carcinoma	65 (9.0)
Adenocarcinoma	413 (57.0)
NSCLC (other)	44 (6.0)
Unknown/missing	3 (0.0)
Stage	
I	220 (30.3)
II	108 (14.9)
III	187 (25.8)
IV	211 (29.0)
Unknown/missing	2
Treatment	
Radiation	348 (49.4)
Chemo	343 (54.3)
Surgery	288 (39.6)

Note: Measures presented as n (%) unless otherwise noted.
[a]Self-reported stroke, arrhythmia, and congestive heart failure.
% pred, percent-predicted; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; PFT, pulmonary function test.

sequentially for screening eligibility. They had a mean ± SD age of 64.5 ± 9.5 years, with more females than males (56.6% versus 43.4%) and the racial majority was White (62.5%) with the remaining 37.5% African American (Table 1). In terms of smoking burden, 69.8% were smokers with more than 30 pack-years and 41.8% of the patients were current smokers. History of CVD was present in 27.5% of the patients. They had a mean percent-predicted FEV1 and DLCO of 73.0 ± 21.8 and 62.8 ± 19.8, respectively. Adenocarcinoma (57.0%) was the most common cancer histology followed by squamous cell carcinoma (28.0%). In terms of treatment, 49.4%, 54.3%, and 39.6% of the patients received radiation, chemotherapy, and surgery, respectively.

Starting with the USPSTF 2013 reference group, 370 of patients qualified. The remaining patients were assessed for both USPSTF 2021 and NCCN gp 2 criteria, of which 121 and 155 patients qualify for screening under each set of criteria, respectively. For the comparison with the PLCOm2012 criteria, all patients with missing education data needed for PLCOm2012 risk calculation were excluded, leaving 283 patients in the USPSTF 2013 group. The rest of the patients were assessed for PLCOm2012 eligibility of whom 118 patients qualified.

The fixed criteria comparisons using USPSTF 2013 criteria as reference versus USPSTF 2021 and NCCN gp 2 criteria are found in Table 2. The mean age of patients in the USPSTF 2013 group was 66.0 ± 6.3, which was similar to the NCCN gp 2 group (66.0 ± 11.0) and the USPSTF 2021 group was significantly younger (59.6 ± 9.0). The USPSTF 2013 group had the heaviest pack years smoked at 62.1 ± 25.9 compared with 40.5 ± 20.4 in the NCCN gp 2 group and 36.2 ± 19.8 in the USPSTF 2021 group. The proportions of smokers with pack-years 20 to 29 were 55.4% and 38.1% in the USPSTF 2021

Table 2. Pulmonary Comorbidity Measures in INHALE Ever-Smoker Lung Cancer Cases Who Were Either Eligible for USPSTF 2013 or USPSTF 2021 and NCCN Group 2 (N = 561)

Variable	USPSTF 2013 N = 370	USPSTF 2021 N = 121	*p* (USPSTF 2013 vs. 2021)	NCCN group 2 N = 155	*p* (USPSTF 2013 vs. NCCN group 2)
Age, mean (SD)	66.0 (6.3)	59.6 (9.0)	<0.01	66.0 (11.0)	0.97
Pack-years, mean (SD)	62.1 (25.9)	36.2 (19.8)	<0.01	40.5 (20.4)	<0.01
Pack-years					
<20	0	0		0	
20-29	0	67 (55.4)	<0.01	59 (38.1)	<0.01
≥30	370 (100.0)	54 (44.6)		96 (61.9)	
History of CVD					
No	239 (69.1)	88 (75.9)	0.16	104 (71.7)	0.56
Yes	107 (30.9)	28 (24.1)		41 (28.3)	
FEV1/FVC <0.7					
No	109 (29.5)	54 (44.6)	<0.01	67 (43.2)	<0.01
Yes	261 (70.5)	67 (55.4)		88 (56.8)	
% pred FEV1 <50%					
No	295 (79.7)	107 (88.4)	0.03	135 (87.1)	0.05
Yes	75 (20.3)	14 (11.6)		20 (12.9)	
% pred DLCO <50%					
No	214 (70.9)	86 (81.1)	0.04	99 (77.9)	0.13
Yes	88 (29.1)	20 (18.9)		28 (22.1)	
History of COPD					
No	177 (49.4)	74 (62.7)	0.01	85 (55.9)	0.18
Yes	181 (50.6)	44 (37.3)		67 (44.1)	
Any COPD[a]					
No	76 (20.5)	40 (33.1)	<0.01	49 (31.6)	0.01
Yes	294 (79.5)	81 (66.9)		106 (68.4)	

[a]Either self-reported history of COPD or FEV1/FVC <0.7 on spirometry.

% pred, percent-predicted; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; INHALE, INflammation, Health, Ancestry and Lung Epidemiology; NCCN, National Comprehensive Cancer Network; USPSTF, U.S. Preventive Services Task Force. Frequencies presented as N (%).

group and the NCCN gp 2 group, respectively. History of CVD was present in 30.9% of the USPSTF 2013 patients and was lower in the NCCN gp 2 group and the USPSTF 2021 group, at 28.3% and 24.1%, respectively, but these differences were not statistically significant. Airway obstruction defined as FEV1/FVC less than 0.7 was present in 70.5% of the patients in USPSTF 2013 which was significantly higher compared with 55.4% and 56.8% in USPSTF 2021 and NCCN gp 2, respectively. We measured the severity of airflow obstruction by evaluating the FEV1. The number of patients with FEV1 less than 50% was almost double and statistically higher in the USPSTF 2013 group at 20.3% compared with 11.6% and 12.9% in the USPSTF 2021 group and the NCCN gp 2 group, respectively. Similarly, the number of patients with DLCO less than 50% was 29.1% in the USPSTF 2013 group which was significantly higher than 18.9% in the USPSTF 2021 group but not statistically significant when compared with 22.1% in the NCCN gp 2 group. Figure 2*A* and *B* illustrates the distribution of FEV1 and DLCO (in 10% increments) among patients selected by the different screening criteria. History of COPD based on patient's self-reporting was present in 50.6% of patients in the USPSTF 2013 group which was significantly higher than that of 37.3% in the USPSTF 2021 group but not significantly different compared with 44.1% in the NCCN gp 2 group. Presence of COPD based on either spirometry or self-reporting (any COPD) was 79.5% in the USPSTF 2013 group, which was significantly higher than 66.9% and 68.4% in the USPSTF 2021 group and the NCCN gp 2 group, respectively.

The prediction model risk-based criteria comparison consisted of 283 patients in the USPSTF 2013 group versus 118 patients in the PLCOm2012 group. Patients in the PLCOm2012 were of similar age compared with patients in the USPSTF 2013 group (67.6 ± 10.6 versus 65.7 ± 6.1, $p = 0.06$) (Table 3). Only half of the patients in the PLCOm2012 group were smokers of 30 pack-years and above. The mean pack-year was significantly lower in the PLCOm2012 group compared with the USPSTF 2013 group (38.8 ± 21.8 versus 59.8 ± 22.9, $p < 0.01$). History of CVD was present in 29.7% and 30.5% of patients in the USPSTF 2013 group and the PLCOm2012 group, respectively, which was not statistically different. Airway obstruction (FEV1/FVC < 0.7) was present in 68.9% of patients in the USPSTF 2013 group and was lower in the PLCOm2012 group at 60.2% but was not statistically significant. In terms of severity of airflow

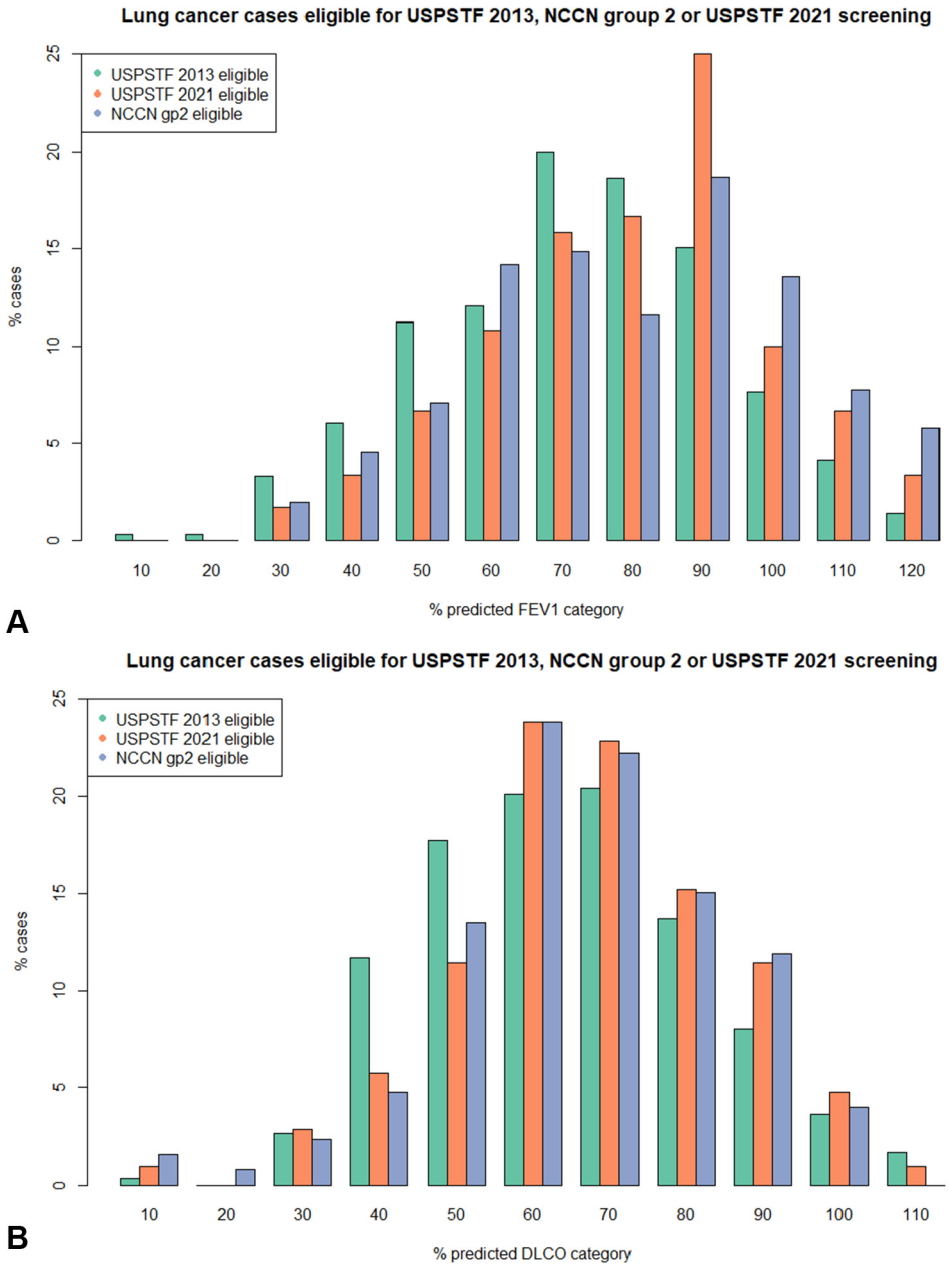

Figure 2. Pulmonary function test results for patients selected by different lung screening criteria. (*A*) Percent-predicted FEV1 distribution and (*B*) percent-predicted DLCO distribution. Grouping of patients per Table 2: USPSTF 2013, n = 370; NCCN gp2, n = 155; USPSTF 2021, n = 121. DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; NCCN gp2, National Comprehensive Cancer Network group 2; USPSTF, U.S. Preventive Services Task Force.

obstruction, the USPSTF 2013 group had twice the number of patients with percent-predicted FEV1 less than 50% than PLCOm2012 (22.3% versus 10.2%, $p < 0.02$). The USPSTF 2013 group also had significantly more patients with DLCO less than 50% compared with PLCOm2012 (32.6% versus 20.0%, $p = 0.01$). There were no significant differences between the USPSTF 2013 group and the PLCOm2012 group in the number of patients having COPD based on self-report or spirometry (history of COPD or any COPD).

Discussion

Our analysis described the cardiopulmonary comorbidities of patients selected by the original USPSTF 2013 versus additional patients selected by the newer USPSTF 2021 with a lower age and smoking threshold. As expected, a younger and healthier cohort of patients was selected with better lung function and lower rates of COPD which will likely be associated with better surgical outcomes. The NCCN gp 2, which has the same age and smoking requirement as USPSTF 2021 but with

Table 3. Pulmonary Comorbidity Measures in INHALE Ever-Smoker Lung Cancer Cases Who Were Either Eligible for USPSTF 2013 or PLCO 2012 (N = 401)

Variables	USPSTF 2013 N = 283	PLCOm2012 N = 118	*p* (USPSTF 2013 vs. PLCOm2012)
Age, mean (SD)	65.7 (6.1)	67.6 (10.6)	0.06
Pack-years, mean (SD)	59.8 (22.9)	38.8 (21.8)	<0.01
Pack-years			
<20	0	11 (9.3)	
20-29	0	43 (36.4)	<0.01
≥30	283 (100.0)	64 (54.2)	
History of CVD			
No	199 (70.3)	82 (69.5)	0.87
Yes	84 (29.7)	36 (30.5)	
FEV1/FVC < 0.7			
No	88 (31.1)	47 (39.8)	0.09
Yes	195 (68.9)	71 (60.2)	
% pred FEV1 < 50%			
No	220 (77.7)	106 (89.8)	<0.01
Yes	63 (22.3)	12 (10.2)	
% pred DLCO < 50%			
No	149 (67.4)	76 (80.0)	0.02
Yes	72 (32.6)	19 (20.0)	
History of COPD			
No	151 (53.4)	73 (61.9)	0.12
Yes	132 (46.6)	45 (38.1)	
Any COPD[a]			
No	68 (24.0)	34 (28.8)	0.32
Yes	215 (76.0)	84 (71.2)	

Note: Frequencies presented as N (%).
[a]Either self-reported history of COPD or FEV1/FVC <0.7 on spirometry.
% pred, percent-predicted; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; INHALE, INflammation, Health, Ancestry and Lung Epidemiology; USPSTF, U.S. Preventive Services Task Force.

additional risk factor requirements such as COPD, has similarly good PFT results as USPSTF 2021. Nonetheless, the rate of self-reported COPD was closer to the group defined under the USPSTF 2013. Comparison of the USPSTF 2013 with the prediction model risk-based criteria PLCOm2012 found that the PLCOm2012 in our cohort also selected an equally older aged group of patients with similar COPD burden as USPSTF 2013. Nonetheless, they have better lung reserve evidenced by lower rates of FEV1 or DLCO less than 50%.

Even with mild COPD, patients have a higher prevalence of postoperative complications compared with patients with normal spirometry results.[15] Common postoperative complications include pneumonia, atelectasis, prolonged air leak, empyema, and need for tracheostomy. Post hoc analysis of the NLST revealed that mortality reduction with LDCT screening in participants with COPD was only half of the mortality reduction in participants without COPD (15% versus 28%, respectively).[9,16] This may be due to competing causes of death, such as CVD. In our cohort, the heavy smoking burden required by the USPSTF 2013 selected almost 80% of patients with COPD compared with the lower proportion in USPSTF 2021 and NCCN gp 2 (66%–67%).

Nonetheless, among patients with COPD, it is more beneficial to screen patients with milder COPD than more severe COPD. The study by de-Torres et al.[17] revealed that LDCT screening in mild to moderate COPD results in early, curable stages and better long-term survival. In contrast, other competing causes of death inherent to COPD increase with worsening airflow obstruction.[18] We found that although USPSTF 2013 and PLCOm2012 select patients very differently (fixed criteria versus prediction risk model based), both criteria select patients with similar age and similar proportion of having COPD. The difference here is the severity of airflow obstruction (FEV1); the USPSTF 2013 selected double the number of patients with FEV1 less than 50% compared with PLCOm2012 (20.3% versus 11.6%). This is also reflected in the number of patients with DLCO less than 50%. Although the patients in PLCOm2012 are of similar age, half of the group had less than 30 pack-years of smoking. The International Lung Screening Trial comparing the USPSTF 2013 versus PLCOm2012 in screening eligibility found that the PLCOm2012-selected patients were older and had more comorbidities.[19] The difference in finding can be attributed to the International Lung Screening Trial study only

including patients aged 55 to 80 years for the PLCOm2012 group when the PLCOm2012 can identify additional high-risk patients outside of this age range.

A lung cancer-screening patient should expect to lose 10% to 26% (2–5 lobes) of their lung function if they undergo at least a lobar resection from a positive screening result. We selected 50% prediction as the cutoff for evaluating our patients' FEV1 and DLCO because that will give a PPO value of 40%, assuming 20% loss in lung function. In-hospital mortality has been reported to be 14% in patients with PPO FEV1 less than 40%.[20] Patients found to have lung cancer by screening tend to be of early stage. Among patients with stage 1 NSCLC and COPD, patients with PPO FEV1 less than 40% had a 35% survival rate compared with 65% in patients with PPO FEV1 more than 40%.[21]

The 2013 Chest guideline recommends cardiopulmonary testing to determine patients' exercise capacity if either of their PPO FEV1 or DLCO is less than 30%. Using a 40% cutoff for FEV1 and DLCO will give a PPO of 30% assuming a loss of 25% with resection. Figure 2*A* and *B* illustrates the distribution of FEV1 and DLCO among the patients selected by different criteria, respectively. FEV1 less than 40% was present in 10%, 7%, and 7% of patients in USPSTF 2013, USPSTF 2021, and NCCN gp 2 groups, respectively, which potentially disqualify them for lung resection surgery. DLCO less than 40% was present in 15%, 10%, and 10% of USPSTF 2013, USPSTF 2021, and NCCN gp 2 groups, respectively. Hence, the USPSTF 2013 is more likely than other criteria to select patients ineligible for lung resection surgery.

The PLCOm2012 criteria, based on a logistic regression lung cancer risk prediction model that includes age, smoking burden, and sociodemographic risk factors, qualify a patient for screening on the basis of a risk threshold of 1.51%/6 years.[22] Patients reach the threshold by being older, having a heavy smoking burden, having COPD, or having certain sociodemographic risk factors. The recent CISNET lung cancer simulation model revealed the equivalence of 1.70% with USPST 2013 and 1.2% threshold with USPSTF 2021.[23] We used the NLST-derived 1.51% threshold which has been established for a longer time to allow for generalizability with other published studies.[22] Excluding the overlap with the USPSTF 2013 group, the PLCOm2012 criteria tend to select an equally older group of patients as the USPSTF 2013 which may pose a problem with surgical outcomes. Mortality from thoracotomy increases with age. The 30-day mortality is as low as 0.4% for patients younger than 60 years, goes up to 2.0% for patients aged 70 to 79 years, and is as high as 2.2% for those aged 80 years or older.[24] Nonetheless, the surgical approach for lung cancer resection is moving away from open thoracotomy to thoracoscopic surgery owing to the increasing acceptance that it offers similar oncologic efficacy and with fewer complications.[25] The use of thoracoscopic surgery halved the risk of postoperative pneumonia compared with open thoracotomy.[26]

Overdiagnosis, which is the detection of an indolent cancer that would not otherwise become clinically apparent, is an inherent problem with lung cancer screening. Approximately 18% of cancer detected in the NLST was determined to be overdiagnosis, with most being bronchioalveolar carcinoma (now reclassified).[27,28] Nonetheless, the overdiagnosis rate decreases to 3% on extended follow-up.[29] Detection of patients with such indolent cancer can artificially increase the survival rates for lung cancer. Lead time bias occurs because these patients are unlikely to die from the cancer during the study period.[16] The analysis of the American College of Radiology Imaging Network cohort of the NLST found that the excess cancer detected was attributed to bronchioalveolar carcinoma that was mainly in subjects without COPD rather than subjects with COPD.[30] This reveals that screening subjects with COPD can result in more cancer detected per person while minimizing overdiagnosis. In our study cohort, among all the screening criteria, the PLCOm2012 fits this unique characteristic of having more patients with COPD and at the same time only having mild to moderate airflow limitation (FEV1 $>$50%). Nevertheless, the CISNET lung cancer simulation model indicates that risk model-based criteria (PLCOm2012) shifted screening to older age and that the criteria were more susceptible to overdiagnosis compared with risk factor-based criteria (USPSTF 2013).[23]

The inherent strength of our study is the use of a cohort of patients with known lung cancer rather than a large cohort of patients undergoing screening of whom only a small fraction will develop cancer. This is because ultimately it is the patients with lung cancer in whom surgical fitness matters. At the same time, the use of a cohort of patients with known lung cancer to represent the potential distribution of cardiopulmonary comorbidity of an actual lung cancer screening cohort has its limitations. A patient may have a better PFT if the lung cancer is diagnosed early by screening compared with the cancer manifesting overtly at a more advance stage allowing for the further decline in lung reserve especially with continual cigarette exposure.

The USPSTF 2013 criteria are the most recommended lung cancer screening criteria among the major organizations in the United States albeit with small differences in the upper age limit. The introduction of USPSTF 2021 qualifies a larger group of screening candidates who are healthier with better lung reserve translating to better

surgical candidacy. The PLCOm2012 guidelines, which are known to have better accuracy in selecting patients at risk of cancer, select an older group with COPD but with still having good lung reserve.

CRediT Authorship Contribution Statement

Chan Yeu Pu: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Roles/Writing—original draft, Writing—review and editing.

Christine M. Lusk: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Roles/Writing—original draft, Writing—review and editing.

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