## Underreporting of Interstitial Lung Abnormalities on Lung Cancer Screening Computed Tomography

*To the Editor*:

Interstitial lung abnormality (ILA), defined as subclinical bilateral interstitial densities on computed tomography (CT) scan of the chest, are observed in up to 10% of CT scans performed for lung cancer screening (1, 2). Despite evidence that those with ILA are at increased risk of death, hospitalization, and pulmonary function decline (3, 4), current management practices remain uncharacterized. In this multicenter investigation, we assess the reporting of ILA by radiologists reading lung cancer screening CT scans and subsequent management of these patients by primary care physicians.

### Methods

This retrospective investigation was conducted at the University of California at Davis and The University of Chicago. Institutional review boards at each institution approved the study and provided a waiver of consent. Radiology databases were used to identify consecutive lung cancer screening CT scans performed from January 1, 2014, to June 1, 2017. A chest radiologist (M.K. or J.H.C.) with interstitial lung disease multidisciplinary experience reviewed lung cancer screening CT scans at each center to identify ILA, defined as bilateral nondependent reticular opacities. CT scans were also assessed for usual interstitial pneumonia (UIP) subtype (typical UIP, probable UIP, indeterminate for UIP, or inconsistent with UIP) (5), interstitial lung disease features (reticulation, honeycombing, traction bronchiectasis, traction bronchiolectasis, and ground-glass opacity), and concurrent emphysema of 10% or greater involvement. ILA with fibrosis was defined as the presence of honeycombing or traction bronchiectasis or bronchiolectasis.

The electronic medical record was retrospectively reviewed to extract pertinent clinical information, including primary care physicians' documentation and order history that occurred after the lung cancer screening CT scan. Because an aim of the study was to assess pulmonology referral by primary care physicians, patients without an institutional primary care physician and those with an established pulmonologist were excluded. Continuous variables are reported as means with standard deviation. Categorical variables are reported as counts and percentages. The association between ILA reporting by a radiologist and pulmonology referral by a primary care physician was assessed using log-binomial regression, with statistical significance defined as $P < 0.05$. Statistical analysis was performed using Stata (StataCorp 2013, release 13).

### Results

Lung cancer screening CT scans were reviewed for 781 patients, including 364 at University of California at Davis and 417 at The University of Chicago. ILA was detected in 71 (9.1%) cases. Five patients without a primary care physician and seven with an established pulmonologist were excluded, leaving 59 (7.6%) patients included in the final analysis. Cohorts were similar with regard to baseline characteristics, except race distribution, in which white individuals predominated at the University of California at Davis and African Americans at The University of Chicago. The combined cohort mean age was 67.3 years, with 49.2% ($n = 29$) men and 44.1% ($n = 26$) current smokers (Table 1).

ILA was noted in 38 of 59 (64%) lung cancer screening CT reports, with 16 of 38 noted in the findings section alone and 22 of 38 noted in the findings and impression sections. Three patients (5.1%) had a typical UIP pattern, 6 (10.2%) had a probable UIP pattern, 27 (45.8) had an indeterminate for UIP pattern, and 23 (39%) had a pattern inconsistent with UIP. Honeycombing was observed in 14% ($n = 8$) of cases. Concurrent emphysema involving 10% or more of the lungs was observed in 42.5% ($n = 25$) of cases.

Interstitial lung disease was documented and pulmonary function test ordered by primary care physicians in 12% ($n = 7$) of cases. A pulmonology referral was placed in 28% ($n = 17$) of cases. Forty-five percent (10 of 22) of those with ILA mentioned in the lung cancer screening CT report impression received pulmonology referral, compared with 19% (7 of 37) of those without mention (risk ratio, 1.6; 95% confidence interval, 1.0–2.3; $P = 0.03$). This association

**Table 1.** Clinical characteristics of interstitial lung abnormality cohort

| | Not Referred (*n = 42*) | Referred (*n = 17*) | Combined (*n = 59*) |
|---|---|---|---|
| Baseline demographics | | | |
| Male | 20 (47.6) | 9 (52.9) | 29 (49.2) |
| Age, yr, mean ± SD | 67 ± 6.3 | 67.5 ± 6.2 | 67.3 ± 6.2 |
| Race | | | |
| White | 26 (61.9) | 7 (41.2) | 33 (55.9) |
| African American | 14 (33.3) | 9 (52.9) | 23 (39) |
| Hispanic | 0 (0) | 1 (5.9) | 1 (1.7) |
| Asian | 2 (4.8) | 0 (0) | 2 (3.4) |
| Smoking history | | | |
| Current | 16 (38.1) | 10 (58.8) | 26 (44.1) |
| Past | 26 (61.9) | 7 (41.2) | 33 (55.9) |
| Supplemental oxygen use | 3 (7.1) | 1 (5.9) | 4 (6.8) |
| LCS-CT characteristics | | | |
| ILA reported | 27 (64.3) | 11 (64.7) | 38 (64.4) |
| Findings only | 15 (35.7) | 1 (5.9) | 16 (27.1) |
| Findings and impression | 12 (28.6) | 10 (58.8) | 22 (37.3) |
| ILA with fibrosis | 10 (23.8) | 9 (52.9) | 19 (32.2) |
| UIP pattern | | | |
| Typical UIP | 0 (0) | 3 (17.7) | 3 (5.1) |
| Probable UIP | 3 (7.1) | 3 (17.7) | 6 (10.2) |
| Indeterminate for UIP | 22 (52.4) | 5 (29.4) | 27 (45.8) |
| Inconsistent with UIP | 17 (40.5) | 6 (35.3) | 23 (39) |
| Reticulation | 42 (100) | 17 (100) | 59 (100) |
| Honeycombing | 4 (9.5) | 4 (23.5) | 8 (13.6) |
| Traction bronchiectasis | 8 (19.1) | 5 (29.4) | 13 (22) |
| Traction bronchiolectasis | 8 (19.1) | 8 (47.1) | 16 (27.1) |
| Ground-glass opacity | 12 (28.6) | 8 (47.1) | 20 (33.9) |
| Emphysema ⩾ 10% | 16 (38.1) | 9 (52.9) | 25 (42.4) |
| Emphysema reported | 14 (87.5) | 7 (77.8) | 21 (87.5) |
| PCP characteristics | | | |
| ILD mentioned in PCP notes | 2 (4.8) | 5 (29.4) | 7 (11.9) |
| PFT ordered by PCP | 3 (7.1) | 4 (23.5) | 7 (11.9) |

*Definition of abbreviations*: ILA = interstitial lung abnormality; ILD = interstitial lung disease; LCS-CT = lung cancer screening computed tomography; PCP = primary care physician; PFT = pulmonary function test; SD = standard deviation; UIP = usual interstitial pneumonia.
Data presented as n (%) unless otherwise noted.

persisted after adjusting for center, age, sex, race, smoking history, presence of emphysema, and presence of fibrosis (risk ratio, 1.8; 95% confidence interval, 1.1–2.9; $P = 0.02$) (Table 2). Active smoking was associated with decreased pulmonology referral in adjusted analysis (risk ratio, 0.3; 95% CI, 0.1–0.7; $P = 0.01$).

## Discussion

In this investigation, we showed that interstitial lung abnormality was commonly observed on lung cancer screening computed tomography imaging but reported by a radiologist in only 64% of cases. Of those cases with interstitial lung abnormality reported, nearly half were mentioned only in the findings section, which may be missed by clinicians reading only the impression section. In addition, we showed that fewer than 30% of interstitial lung abnormality cases received a pulmonology referral and that reporting of interstitial lung abnormality by a radiologist was associated with a significantly increased likelihood of pulmonology referral. To our knowledge, this study is among the first to explore the practice of interstitial lung abnormality management in an academic setting and underscores the work ahead to improve care for these patients.

Fifteen percent of patients in our cohort had a typical or probable usual interstitial pneumonia pattern, suggesting that a significant minority of patients had undiagnosed idiopathic pulmonary fibrosis (5), assuming known causes of interstitial lung disease were excluded. Idiopathic pulmonary fibrosis is among the most common and deadly forms of interstitial lung disease but now has approved therapy (6), supporting the urgency of early recognition and referral. We also observed that more than 40% of cases had concurrent emphysema. Combined pulmonary fibrosis and emphysema is increasingly recognized as a unique phenotype that may impact outcomes and measures of disease progression (7, 8).

To improve the communication of interstitial lung abnormality observed on lung cancer screening computed tomography to ordering primary care physicians, we suggest standardized use of the Lung-RADS "S" Modifier, which is used to convey significant computed tomography findings unrelated to lung cancer (9). Equally important will be efforts within the pulmonology community to increase awareness among primary care physicians that interstitial lung abnormality warrants evaluation by a pulmonologist. Ideally, such patients would be referred to an interstitial lung disease center of excellence that provides access to a multidisciplinary evaluation and has been linked to improved outcomes (10).

Our study had several limitations. First was the retrospective design, which can only assess association, not causation. Next, despite a multicenter approach, our sample size was small and was limited to patients followed at academic medical centers. In addition, neither center currently has a standardized lung cancer screening program, which may limit the generalizability of our results. A single-reader radiology approach was used in this study, which may have resulted in some false positives, but the consistency of results across centers was reassuring.

**Table 2.** Association between interstitial lung abnormality reporting and pulmonology referral

| | ILA Not Mentioned | ILA Mentioned |
|---|---|---|
| Referred/total | 7/37 | 10/22 |
| Percent referred (95% CI) | 18.9 (8.0–35.2) | 45.5 (24.3–67.8) |
| Unadjusted risk ratio (95% CI) | 1 (Reference) | 1.6 (1.0–2.3) |
| Adjusted* risk ratio (95% CI) | 1 (Reference) | 1.8 (1.1–2.9) |

*Definition of abbreviations*: CI = confidence interval; ILA = interstitial lung abnormality.
*Adjusted for center, age, sex, race, smoking history, presence of emphysema, and presence of fibrosis.

## Conclusions

Interstitial lung abnormality, increasingly shown to be a clinically significant finding (3, 4), is underreported by radiologists and uncommonly referred to pulmonologists after detection by lung cancer screening computed tomography. Because diagnostic and referral delays are common among patients with interstitial lung disease, computed tomography performed for lung cancer screening serves as a valuable opportunity to improve care for these patients.

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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## The Effect of Defining Chronic Obstructive Pulmonary Disease by the Lower Limit of Normal of the $FEV_1/FVC$ Ratio

*To the Editor*:

We read with interest the article by Calverley and colleagues (1), concerning a study of smokers with an $FEV_1/FVC$ ratio lower than 0.70 and a mean age of 65.0 years, in which a risk comparison was made between participants with an $FEV_1/FVC$ at least the lower limit of normal (⩾LLN) versus less than the LLN. We thank the authors for having made this comparison, as it may also inform other chronic obstructive pulmonary disease (COPD)-related studies. However, we have concerns regarding the authors' conclusions. Calverley and colleagues (1) performed a post hoc analysis of data from TIOSPIR (Tiotropium Safety and Performance in Respimat), a randomized clinical trial that enrolled participants with $FEV_1/FVC < 0.70$ and $FEV_1 \leqslant 70\%$ predicted. A substantial proportion of the TIOSPIR participants had obesity (22.3%) and baseline cardiovascular disease (26.1%) and used a pulmonary or cardiovascular medication (90.6% and 51.1%, respectively). Hence, the TIOSPIR study population is at risk of having adverse cardiovascular outcomes, given their obesity, baseline cardiovascular disease, and use of a pulmonary and cardiovascular medication.

In this TIOSPIR cohort (1), when compared with those with $FEV_1/FVC <$ LLN, the participants with $FEV_1/FVC \geqslant$ LLN had higher rates of obesity (37.0% vs. 20.6%), baseline cardiovascular disease (33.0% vs. 25.3%), and use of a cardiovascular medication (65.0% vs. 49.5%). We also note that those with $FEV_1/FVC \geqslant$ LLN frequently used a pulmonary medication (86.1%). Although not reported by the authors, the group with $FEV_1/FVC \geqslant$ LLN likely included some participants with a spirometric restrictive pattern (defined by $FEV_1/FVC \geqslant$ LLN, but $FVC <$ LLN), which has been shown to be a risk factor for adverse cardiovascular events (2). The authors' results are also difficult to interpret because of the omission of the prevalence of hypertension in their groups, which is a major risk factor for cardiovascular disease. We also do not know what strategy was followed for managing cardiovascular risk in all their subjects.

Calverley and colleagues (1) found that TIOSPIR participants with $FEV_1/FVC \geqslant$ LLN had a significantly greater risk for major adverse cardiac events than those with $FEV_1/FVC <$ LLN (there being no difference in mortality), and had a significantly lower risk for COPD exacerbations. Given this observation, the authors surprisingly concluded that the LLN threshold has limitations in establishing airflow obstruction (COPD). This conclusion is not warranted, as the group with $FEV_1/FVC \geqslant$ LLN did not have a normal health status, instead having a high frequency of cardiovascular risk factors that included the inappropriate and potentially harmful use of pulmonary medications (3), and also likely included subjects with a restrictive pattern, another potential cardiovascular risk factor (2). A more logical conclusion from their findings is that those with $FEV_1/FVC <0.7$ but ⩾LLN in fact had cardiac disease as their primary condition to account for their symptoms.

Residual confounding resulting from smoking is also an important concern. Because the enrollment criterion for the TIOSPIR trial required a smoking history of at least 10 pack-years (participants averaged 44 pack-years [as per original trial report]), we posit that there is a strong likelihood of residual confounding overwhelming covariate adjustments and being biased toward adverse cardiovascular outcomes, thus limiting the comparisons between $FEV_1/FVC \geqslant$ LLN versus <LLN, as done by Calverley et al in their article and online supplement. A more meaningful comparison would evaluate a study sample that is more representative of the general population, as previously done with the Third National Health and Nutrition Examination Survey (4).

There is already a strong rationale to establish airflow obstruction (COPD) based on the LLN threshold, as defined by a z-score of −1.64 and as calculated by the Global Lung Function Initiative (4–6). Using data from COPDGene, it has been shown that Global Lung Function Initiative-defined airflow obstruction ($FEV_1/FVC <$ LLN) had a strong graded association with dyspnea, respiratory health-related quality of life, exercise capacity, and computed tomography-measured emphysema and gas trapping compared with Global Lung Function Initiative-defined normal spirometry ($FEV_1/FVC, \geqslant$ LLN; FVC, >LLN) (3).

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