CHEST

Original Research

COPD

Emphysema Scores Predict Death From COPD and Lung Cancer

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Objective: **Our objective was to assess the usefulness of emphysema scores in predicting death from COPD and lung cancer.**

Methods: **Emphysema was assessed with low-dose CT scans performed on 9,047 men and women for whom age and smoking history were documented. Each scan was scored according to the presence of emphysema as follows: none, mild, moderate, or marked. Follow-up time was calculated from time of CT scan to time of death or December 31, 2007, whichever came first. Cox regression analysis was used to calculate the hazard ratio (HR) of emphysema as a predictor of death.**

Results: **Median age was 65 years, 4,433 (49%) were men, and 4,133 (46%) were currently smoking or had quit within 5 years. Emphysema was identified in 2,637 (29%) and was a significant predictor of death from COPD (HR, 9.3; 95% CI, 4.3-20.2; $P < .0001$) and from lung cancer (HR, 1.7; 95% CI, 1.1-2.5; $P = .013$), even when adjusted for age and smoking history.**

Conclusions: **Visual assessment of emphysema on CT scan is a significant predictor of death from COPD and lung cancer.**

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Abbreviations: HR = hazard ratio; NDI = National Death Index

COPD is the fourth leading cause of death in the United States and causes > 2.5 million deaths worldwide each year.[1-3] The most frequent cause of death in advanced COPD is respiratory failure, but in mild and moderate COPD, lung cancer and cardiovascular diseases account for two-thirds of the deaths.[4]

GOLD (Global Initiative for Chronic Obstructive Lung Disease) defines COPD as a disease state characterized by the presence of airway obstruction that is not fully reversible.[5] In these patients, airflow obstruction is caused by a mixture of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions vary from person to person. Airway obstruction, readily determined by spirometry, has been shown to predict an increased mortality rate in the general population.[6] Emphysema has been extensively studied physiologically, pathologically, and at autopsy, but not until recent advances in CT scan technology has there been a reliable means for its in vivo diagnosis and characterization. However, data regarding the significance of CT scan-detected emphysema in determining outcomes are scarce. Studies have shown that the presence of emphysema on low-dose chest CT scan in a cohort participating in a lung cancer screening study is an independent risk factor for lung cancer.[7,8] A study that was limited to patients with lung cancer showed that CT scan-detected emphysema, but not airway obstruction, was associated with a worse prognosis.[9]

Recently, the presence of emphysema on a CT scan has been associated with an increase in mortality in a small cohort of patients with COPD, most of whom entered the study in advanced stages of the disease.[10] To date, no relationship between emphysema as identified on chest CT scan and mortality in the general population or in asymptomatic smokers has been reported. In the present study, we explored whether the presence and extent of emphysema detected on low-dose CT scans are risk factors for mortality from COPD or lung cancer among a large cohort of asymptomatic smokers.

Materials and Methods

Subjects

Data for this study were obtained from prospective examination of a cohort of 9,047 asymptomatic men and women at risk for lung cancer who underwent low-dose CT scan screening for lung cancer in New York State in June 2000 to December 2007. This cohort included subjects who were aged 40 to 85 years at the time of enrollment with no prior lung cancer or other cancer (except squamous cell or basal cell skin cancer) who were fit to undergo thoracic surgery. Each participant completed a precoded questionnaire that asked about symptoms that would lead to exclusion from the study: hemoptysis, unexplained weight loss, hoarseness, and worsening cough. In accordance with the protocol for CT scan screening for lung cancer,[9] all participants had an ungated, low-dose CT scan at one of the 12 participating institutions, and all consented according to the approved institutional review board, Health Insurance Portability and Accountability Act-compliant protocol at each institution. If a participant had more than one CT scan during the study period, only the first scan was included for purposes of this report.

Imaging and Reading of the Images

The low-dose CT scan was obtained from the lung apices to the bases in a single breath at maximum inspiration. Cardiac gating and IV contrast material were not used. All interpretations of the chest CT scans used in this report were performed at the coordinating center using standardized criteria. Interpretation was done first by a radiology fellow (A. O. F.) and then confirmed by one of four experienced chest radiologists (D. I. M., M. C., D. F. Y., C. I. H.). The reader viewed the images on a high-resolution monitor at its typical window and level settings with maximum magnification while scrolling through the images one by one. Interpretations were performed using standard lung settings (width, 1,500 Hounsfield units; level, −650 Hounsfield units).

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Extent of Emphysema

A participant was classified as having no emphysema or any emphysema. If emphysema was present, it was rated as mild if no discrete areas of decreased attenuation could be identified on the CT scan, but the blood vessels were splayed, suggesting parenchymal expansion, or there were occasional discrete areas of decreased attenuation. The emphysema was rated moderate if discrete areas of decreased attenuation could be identified that involved less than one-half of the lung parenchyma, and it was rated as marked if discrete areas of decreased attenuation could be identified as involving more than one-half of the lung parenchyma. A score of 0 to 3 was assigned for none, mild, moderate, or marked emphysema, respectively. The four radiologists had been working together on interpreting low-dose CT scans for >5 years and developed the simple criteria regarding the presence or absence and extent of emphysema on low-dose CT scans. The radiologists and radiology fellow reviewed prior low-dose CT scans jointly and agreed to the criteria for the presence and extent of emphysema. The assessment was documented when the screening CT scan was being read.

Pack-Years of Cigarette Smoking

Detailed information about smoking history was obtained at the time of baseline screening and at each subsequent visit using a standardized, interviewer-administered questionnaire. Collected data included the age at which habitual smoking began and whether the participant continued to smoke during the past month. For current smokers, information was obtained on the number of packs of cigarettes per day currently being smoked. For former smokers, the typical number of packs of cigarettes smoked per day and the number of years they smoked were obtained as well as the year when they had quit smoking. These data were translated into the lifetime cumulative number of pack-years of cigarette smoking. For purposes of this report, the number of pack-years of smoking was based on the information obtained at the time of the baseline CT scan.

Deaths

All participants were followed regularly as part of the screening protocol and beyond completion of the study. The date of the last attempted contact and the vital status at that time were recorded. In the case of death, the date and cause of death were obtained from family members, the participant's physician, or both. For further verification, the National Death Index (NDI) was searched using the participant's last name, middle name, first name, sex, social security number, date of birth, race, marital status, father's surname, date of last contact, state of residence, state of birth, and age at death, if applicable, as matching criteria. The final determination of vital status was obtained by combining information from family members, the participant's physician, and the results from the NDI search. For purposes of our analysis, only participants confirmed by family members, the physician, or a definite match from NDI were considered to be deceased. All others were assumed to be living as of December 31, 2007. The cause of death was coded according to the *International Classification of Diseases, 10th Revision*. If the *International Classification of Diseases, 10th Revision* code was J43-J44, the death was recorded as being due to COPD (emphysema, chronic bronchitis, or COPD), and if it was C34, the death was recorded as being due to lung cancer. In three participants, the physician in charge of terminal illness disagree about the NDI cause of death, and in those three cases, physician-reported cause of death was used for purposes of these analyses. The readers were blinded to the cause of death determination for the presence of emphysema or lung cancer on the CT scan. Follow-up time was calculated from time of enrollment to time of death or December 31, 2007, whichever came first. Median follow-up time was 72.0 months (range, 0.0-91.9 months).

Statistical Methods

The distribution of sex, age, pack-years of smoking for all smokers, and years since quitting for former smokers were compared according to the extent of emphysema (none, mild, moderate, or marked) using the χ^2 test. The Kaplan-Meier method was used to estimate survival curves for patients with and without emphysema and according to the extent of emphysema. Survival curves were compared with the log-rank test. Cox regression analysis was used to evaluate the association between the extent of emphysema and survival after adjusting for potential confounders such as age, sex, and smoking history. All statistical analyses were performed with SAS version 9.2 (SAS Institute Inc) and two-sided *P* values.

Results

The median age of the 9,047 asymptomatic participants at the time of screening was 65 years, and median pack-years of smoking was 43 (Table 1); 4,433 subjects (49%) were men, 8,078 (89%) were white, and 8,612 (95%) had completed a high school education. All 9,047 were smokers, with pack-years of smoking < 30 for 2,476 (27%), 30 to 59 for 4,188 (46%), and > 60 for 2,383 (26%). The median pack-years of smoking was higher in men than in women (45 vs 42, $P < .0001$). There were 3,080 participants (34%) who were smoking at the time of the CT scan, and the remaining 5,967 had quit prior to enrollment. For the former smokers, the median years of quitting was 15 (range, 0.0-56 years); 1,053 had quit within 5 years of enrollment, and 1,040 and 3,874 had quit 5 to 10 years and ≥ 11 years prior to enrollment, respectively. Current smokers were slightly younger than former smokers (median age, 64 vs 65 years, respectively).

Emphysema was identified in 2,637 participants (29%) (Table 1). The prevalence of emphysema was higher for men than for women (30% vs 28%, $P = .04$) and present more frequently in current smokers than in former smokers (38% vs 25%, $P < .0001$). The prevalence of emphysema increased with increasing age ($P < .0001$) and with increasing smoking history ($P < .0001$).

There were 47 deaths from COPD and 100 from lung cancer. Unadjusted univariate Kaplan-Meier analyses showed an increased mortality from COPD ($P < .0001$) (Fig 1A) and from lung cancer ($P < .0001$) among patients with emphysema (Fig 2A). Similarly, the mortality from COPD ($P < .0001$) and from lung cancer ($P < .0001$) increased with increasing extent of CT scan-detected emphysema (Figs 1B, 2B). Even when adjusted for potential confounders of age and smoking history (pack-years of smoking and time since quitting for former smokers), the presence of emphysema was a significant predictor of death from COPD (hazard ratio [HR], 9.3; 95% CI, 4.3-20.2; $P < .0001$) (Table 2). When considering the extent of emphysema rather than merely its presence, it was mild in 1,908 participants (21%), moderate in 512 (6%), and marked in 217 (2%), and all three were independent risk indicators for death from COPD (Table 2) when adjusted for potential confounders of age and smoking history.

The presence of emphysema was a significant predictor of death from lung cancer (HR, 1.7; 95% CI, 1.1-2.5; $P = .013$) when adjusted for potential confounders of age, pack-years of smoking, current or had quit smoking within 4 years of enrollment, and had quit 5 to 10 years prior to enrollment (Table 3). When considering the extent of emphysema, only marked emphysema was an independent risk indicator of death from lung cancer (Table 3).

Table 1—*Baseline Characteristics of Study Participants According to the Presence of Emphysema*

Characteristic	Absent	Present	Total
No. subjects	6,410 (71)	2,637 (29)	9,047 (100)
Sex			
Male	3,097 (48)	1,336 (51)	4,433 (49)
Female	3,313 (52)	1,301 (49)	4,614 (51)
Median age (IQR)	64 (61-69)	66 (62-70)	65 (61-69)
Median pack-y (IQR)	39 (25-55)	51 (39-73)	43 (28-61)
Smoking status			
Current smoker	1,924 (30)	1,156 (44)	3,080 (34)
Former smoker			
Quit ≤ 4 y	731 (11)	322 (12)	1,053 (12)
Quit 5-10 y	713 (11)	327 (12)	1,040 (11)
Quit ≥ 11 y	3,042 (47)	832 (32)	3,874 (43)

Data are presented as No. (%), unless otherwise indicated. IQR = interquartile range.

Discussion

The main finding of this study is that the presence of emphysema on an ungated, low-dose chest CT scan is an independent predictor of death from COPD or lung cancer. These data show that in asymptomatic individuals, even the presence of mild emphysema is an imaging marker for increase risk of death. Future studies should evaluate whether early intervention, be it smoking cessation or treatment of COPD, could reduce the risk for early mortality.

Currently, spirometry is the standard method used for diagnosing COPD. However, in recent years, there has been an increase in the use of CT scan for the evaluation of emphysema. Prior studies have shown good anatomic correlations between CT scan and pathology specimens as well as an association between CT scan-detected emphysema with the presence of airway obstruction on spirometry.[11] Additionally,

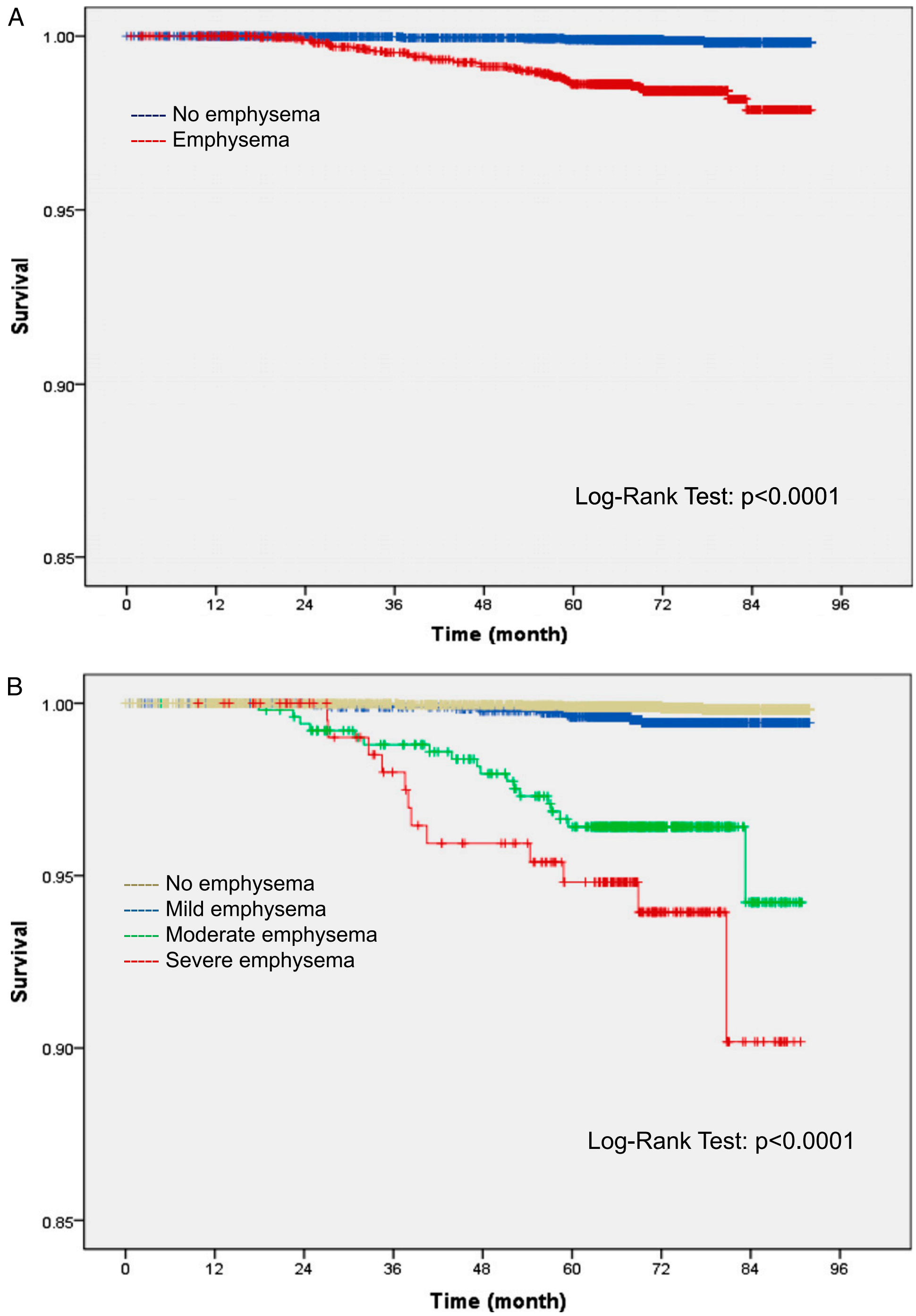

FIGURE 1. Kaplan-Meier curves showing an increase in the COPD-specific deaths for participants with emphysema on CT scans. A, Compared with those without emphysema B, As the extent of emphysema increases.

studies have demonstrated that CT scan-detected emphysema is an independent risk factor for lung cancer.[7,8] The current study expands these findings by showing that individuals with emphysema have an increased risk of death from COPD and lung cancer, further supporting that emphysema on CT scan, even if mild and when patients are asymptomatic, represents genuine lung disease. This is especially relevant when considering that in a similar cohort of asymptomatic smokers for which lung function is available, one-half of the individuals with emphysema on CT scan would not be diagnosed as having COPD according to current diagnostic criteria.[7] The association between COPD and lung cancer, perhaps related to chronic inflammation or changes in bronchial epithelial gene expression, are further strengthened

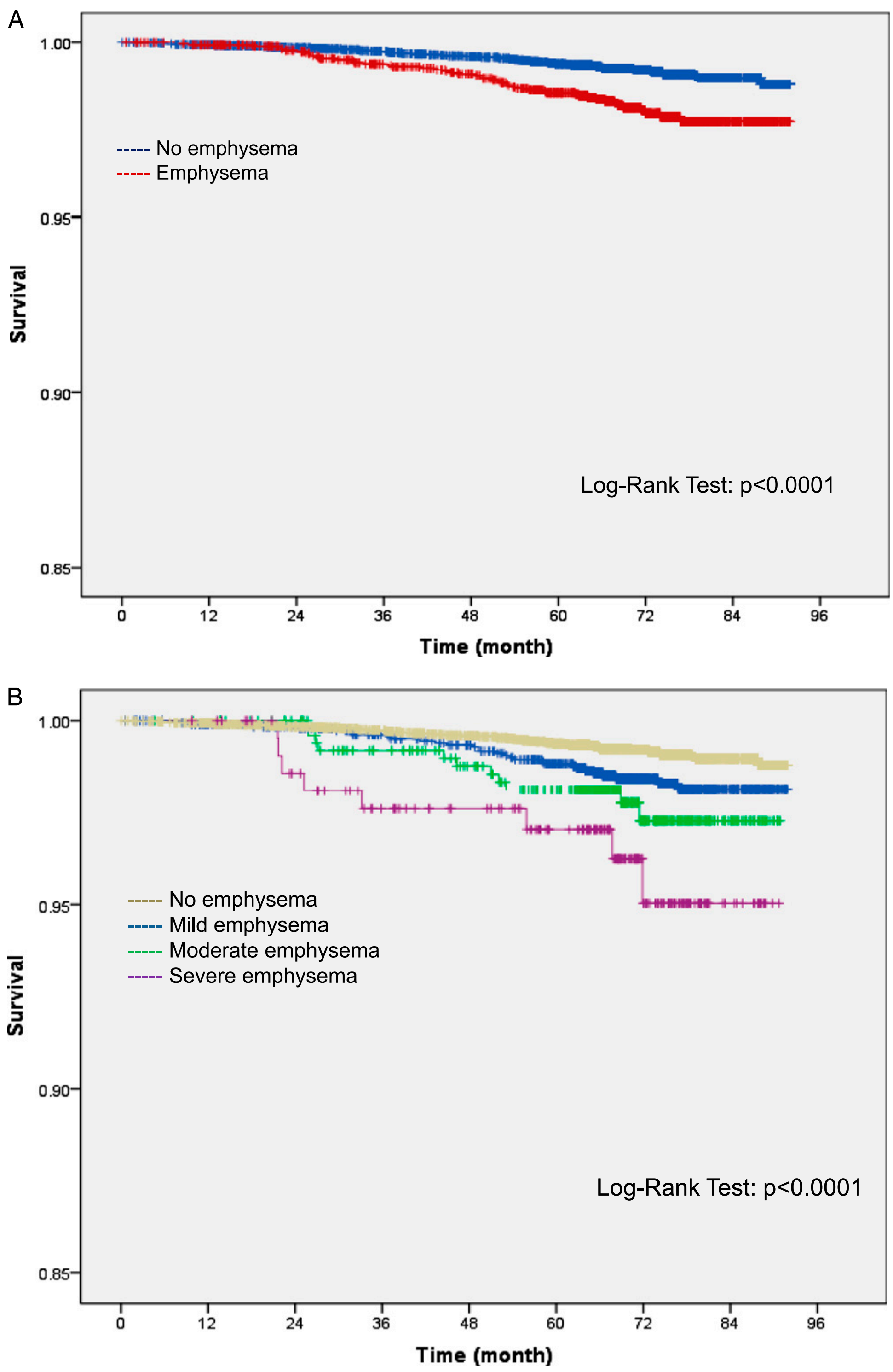

FIGURE 2. Kaplan-Meier curves showing an increase in lung cancer-specific mortality for subjects with emphysema on CT scans. A, Compared with those without emphysema. B, As the extent of emphysema increases.

by the associations between CT scan evidence for emphysema, the diagnosis of lung cancer, and death from COPD and lung cancer.

The current data also show that a considerable proportion of asymptomatic smokers have evidence of some degree of emphysema on CT scan. Approximately one-third of the study cohort had CT scan findings of emphysema, a proportion similar to that found in other lung cancer screening studies from Spain[7] and Japan.[12] As mentioned previously, in one

Table 2—*Adjusted Hazard for Deaths From COPD and Deaths From COPD According to the Extent of Emphysema*

Variables in the Model	HR	95% CI
Emphysema alone	12.2	5.7-26.2
Adjusted for:		
Age	11.1	5.2-23.8
Age and pack-y	10.4	4.8-22.5
Age, pack-y, and smoking status	9.3	4.3-20.2
According to extent of emphysema		
Mild	3.2	1.2-8.3
Moderate	22.3	9.5-52.3
Marked	34.7	13.9-86.6
Age	1.1	1.1-1.2
Pack-y	1.0	1.0-1.0
Current smoker or quit within 4 y	2.4	1.1-5.0
Former smokers who quit 5-10 y prior to study	3.3	1.4-8.0

HR = hazard ratio.

of these studies, one-half of the participants with emphysema (15% of the entire cohort) had normal lung function, and the presence of emphysema was found to predict a diagnosis of lung cancer even among patients with normal spirometry.[7] These results combined highlight the importance of detecting emphysema on CT scan, irrespective of the presence or absence of airflow limitation.

The data also confirm the aforementioned reports linking the presence of CT scan-detected emphysema to an increased risk of lung cancer. Long-term follow-up in the Lung Health Study has shown that lung cancer is the most common cause of death among smokers and former smokers with asymptomatic COPD.[13] Epidemiologic studies have shown that lung function measured by spirometry predicts mortality not only in patients with COPD, but also in the general population.[14-17] Some of these studies show this relationship to hold true independent of smoking status.[17] However, in all these reports, COPD is defined exclusively by airflow limitation, and no consideration is given to the presence or absence of emphysema. The current results, in combination with findings of prior studies,[18] support the concept that the correlation between COPD and lung cancer risk is also valid, and may even be stronger, in the presence of CT scan-detected emphysema.

Table 3—*Adjusted Hazard for Lung Cancer Deaths and Lung Cancer Deaths According to the Extent of Emphysema*

Variables in the Model	HR	95% CI
Emphysema alone	2.3	1.6-3.4
Adjusted for:		
Age	2.1	1.5-3.2
Age and pack-y	1.8	1.2-2.7
Age, pack-y, and smoking status	1.7	1.1-2.5
According to extent of emphysema		
Mild	1.4	0.9-2.3
Moderate	1.8	0.9-3.4
Marked	3.2	1.5-6.7
Age	1.1	1.0-1.1
Pack-y	1.0	1.0-1.0
Current smoker or quit within 4 y	2.4	1.5-4.0
Former smokers who quit 5-10 y prior to study	1.3	0.6-2.7

See Table 2 for expansion of abbreviation.

The findings are important in view of the increased use of CT scan for clinical purposes and, potentially, in the future for more extensive lung cancer screening. First, the presence of emphysema on the CT scan reflects a greater risk for early death from COPD. This information may help in selecting individuals who may benefit the most from smoking cessation and, potentially, from early treatment of COPD. Second, the presence of emphysema provides important information about an individual's risk for lung cancer mortality and their selection as high-risk candidates for early lung cancer detection studies.

The current study has strengths and limitations. Data were obtained from a large sample of asymptomatic volunteers from the general population. The cohort was followed prospectively, which allowed us to assess the long-term outcomes of patients with and without emphysema on CT scan. The study cohort consisted primarily of elderly patients whose smoking exposure ranged from low, moderate, and high levels of tobacco use. Information on cause of death was obtained from death certificates, and inaccuracies of these have been documented. Studies have also shown that COPD frequently is not listed as the cause of death in these patients; thus, mortality from COPD may be underestimated in our sample.[1] It is, therefore, possible that the association between emphysema on CT scan and death from COPD is even stronger than that observed in our cohort. Another limitation may be related to the small number of deaths from COPD in our cohort, although this is expected in a population mostly comprising asymptomatic individuals. In the current report, neither airflow measurements nor CT scan assessment of the airways were used; thus, the focus was on emphysema alone, and comparisons with the predictive potential of airway disease could not be made. Finally, we used visual scores to assess the presence and extent of emphysema, although quantitative standardized assessment with computer algorithms also could be used. However, the advantage in our study is that visual assessment does not require additional software and is simple, and previous studies have shown the validity of this approach.[19-22]

In conclusion, emphysema frequently is present on chest CT scans of smokers and predicts early death from COPD or lung cancer. These data provide strong evidence regarding the validity and utility of the diagnosis of emphysema made through CT scan. Further research is necessary to determine whether early intervention can reduce the risk of death among these patients.

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Dr Zulueta: contributed to the study concept and design, data analysis and interpretation, writing of the manuscript, and editing and approval of the final manuscript.

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