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Emphysema at Baseline Low-Dose CT Lung Cancer Screening Predicts Death from Chronic Obstructive Pulmonary Disease and Cardiovascular Disease Up to 25 Years Later

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See also the editorial by Mascalchi and Diciotti in this issue.

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Background: The prognostic value of baseline visual emphysema scoring at low-dose CT (LDCT) in lung cancer screening cohorts is unknown.

Purpose: To determine whether a single visual emphysema score at LDCT is predictive of 25-year mortality from all causes, chronic obstructive pulmonary disease (COPD), and cardiovascular disease (CVD).

Materials and Methods: In this prospective cohort study, asymptomatic adults aged 40–85 years with a history of smoking underwent baseline LDCT screening for lung cancer between June 2000 and December 2008. Follow-up continued until death, loss to follow-up, or December 31, 2024. Emphysema was assessed at baseline LDCT and scored from 0 (none) to 3 (severe) by one of four experienced chest radiologists. Baseline smoking history and comorbidities were self-reported. Causes of death (International Classification of Diseases, 10th Revision) were obtained from the U.S. National Death Index, physicians, and family. Associations between emphysema and mortality were evaluated using adjusted Cox proportional hazards and adjusted Fine-Gray competing risks models.

Results: Among 9047 participants (4614 female; median age, 65 years [IQR, 61–69 years]; median pack-years of smoking, 43 [IQR, 28–64]), 2637 (29.1%) had emphysema (mild in 1908 [21.1%], moderate in 512 [5.7%], and severe in 217 [2.4%]). Median follow-up was 23.3 years. Emphysema was independently predictive of all-cause mortality (hazard ratio [HR], 1.29; 95% CI: 1.21, 1.38; $P < .001$), COPD mortality (HR, 3.29; 95% CI: 2.59, 4.18; $P < .001$), and CVD mortality (HR, 1.14; 95% CI: 1.01, 1.29; $P = .04$). A dose-response relationship was observed between emphysema severity and both all-cause and COPD mortality, but not CVD mortality. In the adjusted competing risk analysis, emphysema remained associated with COPD mortality (HR, 3.06; 95% CI: 2.40, 3.90; $P < .001$), but not CVD mortality (HR, 1.04; 95% CI: 0.91, 1.18; $P = .59$).

Conclusion: Baseline emphysema at LDCT in a prospective lung cancer screening cohort of asymptomatic adults was predictive of all-cause, COPD, and CVD mortality up to 25 years later.

Supplemental material is available for this article.

Pulmonary emphysema is the abnormal, permanent enlargement of air spaces beyond the terminal bronchiole with alveolar wall destruction, without evident fibrosis (1). Chest CT is the reference standard for noninvasive diagnosis, enabling detection of low-attenuation regions and vascular disruption (2,3). In lung cancer screening participants in the state of New York, 29% of participants had emphysema, which was predictive of chronic obstructive pulmonary disease (COPD)-related mortality (4). Steiger et al found emphysema in 23.8% of 52 726 screened individuals, 76.5% of whom had no prior COPD diagnosis; notably, 2258 (23.6%) had severe emphysema (5). Similarly, in the National Lung Screening Trial, 82% of individuals with emphysema had no prior history of COPD (6), whereas nearly half of the patients with COPD showed minimal or no evidence of emphysema (7,8).

Emphysema has prognostic value independent of spirometric diagnosis of COPD, being associated with exacerbations, lung function decline, lung cancer, and all-cause mortality (9–12). These findings extend to individuals without heavy smoking or known lung disease (13). However, long-term data are limited: only five nonscreening cohorts with 5–12 years of follow-up have assessed emphysema and mortality (12–18), with just one cohort linking it to chronic lower respiratory or lung cancer deaths (13), and there were inconsistent results regarding cardiovascular disease (CVD) deaths (13,16).

Assessment of emphysema is particularly relevant given the recent focus on developing comprehensive heart and lung screening (19). A simplified four-grade visual scoring system was developed by expert consensus in the state of New York before screening implementation (4), offering good reproducibility and early prognostic value (4). Based on this scoring system, our study examines whether a single visual emphysema score at baseline low-dose CT (LDCT) is predictive of 25-year mortality from all causes, COPD, and CVD.

Abbreviations

CAC = coronary artery calcification, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease, HR = hazard ratio, LDCT = low-dose CT

Summary

Emphysema identified at baseline low-dose CT in a lung cancer screening program was predictive of all-cause, chronic obstructive pulmonary disease, and cardiovascular disease mortality 25 years later in 9047 asymptomatic adults with a smoking history.

Key Results

- This prospective lung cancer screening cohort included 9047 asymptomatic adults with a smoking history who underwent baseline low-dose CT and were followed up to 25 years.
- After adjusting for sex, age, pack-years, and years since quitting smoking, emphysema at baseline low-dose chest CT was predictive of all-cause mortality (hazard ratio [HR], 1.29; $P < .001$), chronic obstructive pulmonary disease (COPD) mortality (HR, 3.29; $P < .001$), and cardiovascular disease (CVD) mortality (HR, 1.14; $P = .04$).
- In the adjusted competing risk analysis, emphysema remained associated with COPD mortality (HR, 3.06; $P < .001$), but not CVD mortality (HR, 1.04; $P = .59$).

Materials and Methods

All 9047 lung cancer screening participants included in the current article were previously reported in our earlier publication (4), which focused on the evaluation of the use of a visual emphysema score in predicting death from COPD and lung cancer. The present study extends those findings by reporting the long-term outcomes of these participants up to 25 years. This prospective cohort consisted of 9047 asymptomatic adults who underwent LDCT screening for lung cancer in the state of New York between June 2000 and December 2008, with follow-up through December 31, 2024. At enrollment, participants were aged 40–85 years with current or past cigarette use. All participants provided written informed consent before enrollment, and the Health Insurance Portability and Accountability Act–compliant study protocol was approved by the respective institutional review board of the 12 participating institutions (20–23). Comprehensive smoking history was gathered at baseline screening and during each follow-up visit through a standardized, interviewer-administered questionnaire. Participants also self-reported their comorbidities at the time of baseline LDCT screening. Documented information included the age at which participants began smoking regularly and whether they had smoked in the past month before enrollment. Additional details on smoking history and exclusion criteria are provided in Appendix S1.

CT Protocols and CT-based Visual Emphysema Score

Detailed information on the LDCT acquisition parameters is provided in Appendix S1 and as previously described (20,23). Initial image interpretation was performed by a radiologist at each institution and reviewed centrally by one of the four experienced chest radiologists (with more than 25 years of experience at the time of the review) (4). These four chest radiologists, who conducted the central review, had collaborated on LDCT interpretation for more than 10 years and developed standardized criteria for assessing the emphysema categories (4).

Participants were categorized as having no emphysema or having mild, moderate, or severe emphysema. When present, emphysema was mild (Fig 1A) if no distinct regions of reduced attenuation were visible on the CT scan, but vascular splaying indicates parenchymal expansion, or if only occasional discrete low-attenuation regions were observed. Moderate emphysema (Fig 1B) was defined by the presence of identifiable low-attenuation regions affecting less than half of the lung parenchyma, whereas severe emphysema (Fig 1C) was defined by the presence of identifiable low-attenuation regions involving more than half of the lung parenchyma. A scoring system from 0 to 3 was applied, corresponding to none, mild, moderate, and severe emphysema, respectively. These assessments were documented at the time of baseline screening CT scan interpretation.

This standardized visual scoring system was applied across the entire lung rather than on a section-by-section basis (24), which reduced complexity and interreader variability. Trained radiologists harmonized their assessments using broad categories, which also reduced interreader variability. This visual scoring system has been widely used in routine clinical practice and has shown superiority over quantitative analysis (20). Prior analysis in a Spanish study also demonstrated excellent interreader agreement for this visual emphysema scoring system (25). Moreover, baseline emphysema scoring in this cohort has demonstrated predictive value for short-term outcomes using the National Death Index data from the 2012 publication (4), as well as for long-term outcomes.

Coronary Artery Calcification Score

Coronary artery calcification (CAC) score was assessed using standard mediastinal settings (width, 350 HU; level, 50 HU). Each of the four major coronary arteries (left main, left anterior descending, left circumflex, and right) was scored by a radiologist as absent (score 0), mild (score 1), moderate (score 2), or severe (score 3) (23). Mild calcification involved less than one-third of the artery length, moderate calcification involved one-third to two-thirds of the artery length, and severe calcification involved more than to two-thirds of the artery length. The sum of scores across arteries yielded an ordinal CAC score (range, 0–12). Participants were categorized into low (score, 0), intermediate (score, 1–3), and high (score, 4–12) CVD risk categories, shown to correlate with Agatston categories: 0 (low risk), 1–400 (intermediate risk), and more than 400 (high risk) (20,26,27).

Deaths

All screening participants were followed up annually by the principal investigator and the study coordinator at each participating institution, who submitted the information required by the common standardized protocol (23). Date and cause of death were obtained from the U.S. National Death Index. In cases of known participant death, details including date and cause of death were also obtained from their physician and family. All others were assumed to be living as of December 31, 2024. The cause of death was coded according to the International Classification of Diseases, 10th Revision (ICD-10). For this analysis, deaths due to all causes were

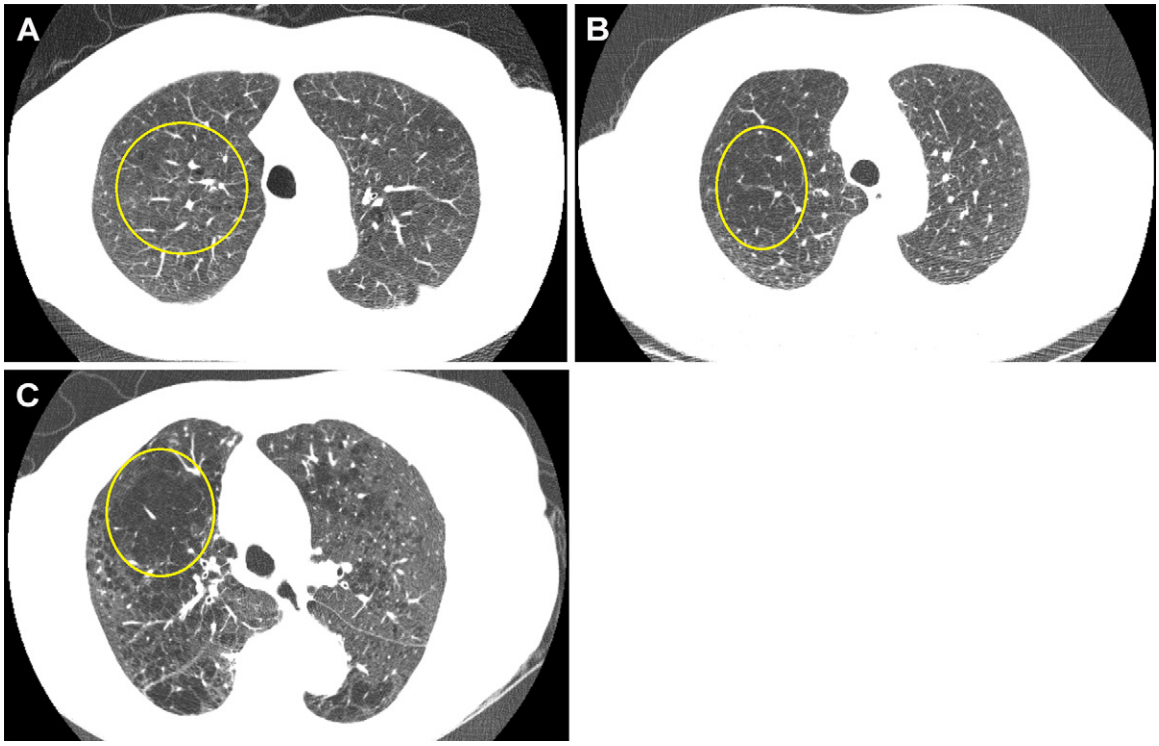

Figure 1: Representative axial images of mild, moderate, and severe emphysema at baseline low-dose CT (LDCT). Participants were categorized as having no emphysema or mild, moderate, or severe emphysema. When present, emphysema was mild if no distinct regions of reduced attenuation were visible on the CT scan, but vascular splaying indicates parenchymal expansion, or if only occasional discrete low-attenuation regions were observed. Moderate emphysema was defined by the presence of identifiable low-attenuation regions affecting less than half of the lung parenchyma, whereas severe emphysema was defined by the presence of identifiable low-attenuation regions that involved more than half of the lung parenchyma. A scoring system from 0 to 3 was applied, corresponding to none, mild, moderate, and severe emphysema, respectively. Yellow circle indicates the extent of emphysema. **(A)** A 67-year-old man with mild emphysema at baseline LDCT in 2002. Baseline LDCT scan shows vascular splaying, suggesting parenchymal expansion due to emphysema and occasional discrete low-attenuation regions. The participant ultimately died of cardiovascular disease 15.4 years (184.2 months) later. **(B)** A 69-year-old man with moderate emphysema at baseline LDCT in 2007. The participant died of cardiovascular disease 1.8 years (21.9 months) later. Identifiable low-attenuation regions affected less than half of the lung parenchyma. **(C)** An 85-year-old woman with severe emphysema at baseline LDCT in 2006. After 5.5 years (65.5 months) of follow-up, the participant died due to chronic obstructive pulmonary disease–related causes. Identifiable low-attenuation regions involved more than half of the lung parenchyma.

considered, and deaths due to COPD (ICD-10 codes J43–J44) and CVD (ICD-10 codes I00–I99) were assessed separately. Follow-up time was calculated from the time of the first LDCT to the time of death, loss to follow-up, or December 31, 2024, whichever came first.

Statistical Analysis

Analyses examined emphysema and all-cause mortality among 9047 participants by ordinal emphysema scores and other risk factors. Continuous variables, including age, pack-years of smoking, and years of quitting smoking before enrollment for participants with a past smoking history, were summarized using medians and IQRs, whereas categorical variables, such as sex and emphysema categories, were summarized as frequencies and percentages. Differences between groups were evaluated using χ^2 tests or Fisher exact tests for categorical variables and *t* tests or Mann-Whitney tests for continuous variables.

To account for censoring and better reflect follow-up among survivors, median follow-up time was also estimated using the reverse Kaplan-Meier method, which treats death as censored, to estimate follow-up among survivors. The association between emphysema scores and mortality outcomes was analyzed using multivariable Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% CIs. Model 1 included emphysema alone, model 2 adjusted for sex and age, model 3 further adjusted for pack-years, and model 4 additionally adjusted for smoking status (current, former) and time since quitting smoking. Model 5 adjusted for the same covariates as model 4 but examined the effect of the extent of emphysema based on the emphysema score categories (none, mild, moderate, and severe), reporting HRs separately for each level. Participants without emphysema served as the reference group for HR comparisons. Trends in mortality risk with increasing emphysema scores were assessed using Cochran-Armitage trend tests. COPD, CVD, and overall survival were estimated using Kaplan-Meier analyses, stratified by emphysema categories. To account for competing risks, we used the Fine-Gray subdistribution hazard model for COPD- and CVD-related mortality, treating deaths from non-COPD and non-CVD as competing events, respectively. This approach allows for direct interpretation of the effect of emphysema on the cumulative incidence function of each cause-specific mortality. Results were compared with the cause-specific hazard models, where competing events are treated as censored observations. For all analyses, *P* values less than or equal to .05 were considered to indicate a statistically significant difference. All statistical analyses were performed using SAS software (version 9.4; SAS Institute).

Table 1: Demographics, Comorbidities, and Extent of Emphysema at Enrollment and CAC at Baseline Low-Dose CT in Lung Cancer Screening Participants

Characteristic	Total No. of Participants (n = 9047)	Female Participants (n = 4614)	Male Participants (n = 4433)	P Value (Female vs Male Participants)
Age (y)*	65 (61–69)	65 (61–69)	65 (61–69)	.15
Smoking status				
Current smoker	3080 (34.0)	1661 (36.0)	1419 (32.0)	<.0001
Former smoker	5967 (66.0)	2953 (64.0)	3014 (68.0)	
Pack-years of smoking*	43.2 (28.0–60.4)	42 (27.0–57.0)	45 (29.0–64.5)	<.0001
Smoking quit time among participants who previously smoked (y)*	15 (7–25)	15 (6–23)	16 (8–26)	
Self-reported comorbidities				
COPD	1135 (12.5)	646 (14.0)	489 (11.0)	<.0001
Diabetes mellitus	630 (7.0)	230 (5.0)	400 (9.0)	<.0001
Vascular diseases	280 (3.1)	122 (2.6)	158 (3.6)	.012
Cardiac diseases	20 (0.2)	3 (0.1)	17 (0.4)	.001
Other diseases	1804 (19.9)	985 (21.3)	819 (18.5)	.0006
Emphysema				
None	6410 (70.9)	3313 (71.8)	3097 (69.9)	.22
Mild	1908 (21.1)	939 (20.4)	969 (21.9)	
Moderate	512 (5.7)	257 (5.6)	255 (5.8	
Severe	217 (2.4)	105 (2.3)	112 (2.5)	
CAC				
None	3719 (41.1)	2336 (50.6)	1383 (31.2)	<.0001
1–3	3662 (40.5)	1693 (36.7)	1969 (44.4)	
4–12	1666 (18.4)	585 (12.7)	1081 (24.4)	

Note.—Pack-years of smoking reflect pack-years among participants who currently smoke or had previously smoked. Unless otherwise indicated, data are numbers of participants, with percentages in parentheses. Participants were categorized as having no emphysema or mild, moderate, or severe emphysema. When present, emphysema was mild if no distinct regions of reduced attenuation were visible on the CT scan, but vascular splaying indicates parenchymal expansion, or if only occasional discrete low-attenuation regions were observed. Moderate emphysema was defined by the presence of identifiable low-attenuation regions affecting less than half of the lung parenchyma, whereas severe emphysema was defined by the presence of identifiable low-attenuation regions involving more than half of the lung parenchyma. A scoring system from 0 to 3 was applied, corresponding to none, mild, moderate, and severe emphysema, respectively. CAC score in each artery (left main, left anterior descending, left circumflex, and right) was scored as absent (score 0), mild (score 1), moderate (score 2), or severe (score 3) by the radiologists (23). Mild calcification was defined if less than one-third of the length of the entire artery showed calcification, moderate when one-third to two-thirds showed calcification, and severe when more than two-thirds showed calcification. With four arteries thus scored, each participant received an ordinal CAC score ranging from 0 to 12. Three ordinal CAC score categories were defined as 0, 1–3, and 4–12 corresponding to low-, intermediate-, and high-risk cardiovascular disease categories, respectively. CAC = coronary artery calcification, COPD =chronic obstructive pulmonary disease.

* Data are medians, with IQRs in parentheses.

Results

Study Cohort Characteristics

Between June 2000 and December 2008, baseline LDCT was performed in 9047 participants (4614 female and 4433 male). Participants had a median age of 65 years (IQR, 61–69 years) and a median smoking history of 43.0 pack-years (IQR, 28–60.4 pack-years) (Table 1). Other specific details on patient characteristics are provided in Table 1. Those who currently smoked were slightly younger than those with a past smoking history (median age, 64 vs 65 years). Among the 9047 participants, 6410 (70.9%) had no evidence of emphysema and 1908 (21.1%) had mild, 512 (5.7%) had moderate, and 217 (2.4%) had severe emphysema (Table 1).

Emphysema Diagnoses and Severity

More male participants were diagnosed with emphysema than female participants (1336 of 4433 [30.1%] vs 1301 of 4614 [28.2%]; P = .04), and emphysema was more frequent in those who currently smoked than in those with a past smoking history (1156 of 3080 [37.5%] vs 1481 of 5967 [24.8%]; P < .001). Additionally, evidence of emphysema increased with advancing age (P < .001) and greater cumulative smoking exposure (P < .001). Of 2637 participants, 2063 (79.2%) with emphysema at baseline LDCT had no prior known diagnosis of emphysema or COPD, even though 103 (5.0%) had moderate or severe emphysema. The frequency of a non-zero CAC score increased (P < .001) with increasing emphysema scores; 55.3% (3542 of 6410) of participants had no emphysema, 66.6% (1270 of 1908) had mild emphysema, 70.1% (359 of 512) had moderate emphysema, and 72.4% (157 of 217) had severe emphysema.

Causes of Death

As of December 31, 2024, 3738 (41.3%) of 9047 participants have died of COPD, CVD, or other causes (Table 2). Median follow-up was 22.5 years (IQR, 14.7–23.5 years). By using the reverse Kaplan-Meier method to account for censoring in the

Table 2: Causes of Death according to Baseline Extent of Emphysema for COPD, CVD, Other Causes, and All Causes in Participants in Programs of Low-Dose CT Screening for Lung Cancer in the State of New York

Extent of Emphysema	Total No. of Participants	COPD Death	CVD Death	Causes Other Than COPD and CVD Death	All Causes of Death
No emphysema	6410	113 (1.8)	772 (12.0)	1403 (21.9)	2376 (37.1)
Emphysema	2637	182 (6.9)	381 (14.4)	717 (27.2)	1362 (51.6)
Mild	1908	83 (4.4)	281 (14.7)	483 (25.3)	899 (47.1)
Moderate	512	56 (10.9)	69 (13.5)	166 (32.4)	307 (60.0)
Severe	217	43 (19.8)	31 (14.3)	68 (31.3)	156 (71.9)
Total	9047	295 (3.3)	1153 (12.7)	2120 (23.4)	3738 (41.3)

Note.—Median follow-up time was 22.5 years (IQR, 14.7–23.5 years). Using the reverse Kaplan-Meier method to account for censoring in the time-to-event analysis framework, the median follow-up time was 23.3 years. Data are numbers of participants, with percentages in parentheses, unless indicated otherwise. Participants were categorized as having no emphysema or mild, moderate, or severe emphysema. When present, emphysema was mild if no distinct regions of reduced attenuation were visible on the CT scan, but vascular splaying indicates parenchymal expansion, or if only occasional discrete low-attenuation regions were observed. Moderate emphysema was defined by the presence of identifiable low-attenuation regions affecting less than half of the lung parenchyma, whereas severe emphysema was defined by the presence of identifiable low-attenuation regions involving more than half of the lung parenchyma. A scoring system from 0 to 3 was applied, corresponding to none, mild, moderate, and severe emphysema, respectively. COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease.

time-to-event analysis framework, the median follow-up time was 23.3 years. CVD deaths occurred in 1153 participants (12.7%), followed by COPD deaths in 295 (3.3%). The median age at death from all causes was 81 years, and that for COPD, CVD, and other causes was 81, 82, and 81 years, respectively.

Unadjusted Survival Rates for All Causes, COPD, and CVD

Figures 2–4 demonstrate different unadjusted survival rates ($P < .001$) among 9047 participants for all causes (or overall survival) (Fig 2), COPD (Fig 3), and CVD (Fig 4) by the presence or absence of emphysema and also for the extent of mild, moderate, and severe emphysema. Overall survival was 48.1% (95% CI: 46.2, 50.0) among those with emphysema and 62.5% (95% CI: 61.2, 63.7) among those without emphysema. Overall survival was 52.6%, 39.9%, and 28.0% for mild, moderate, and severe emphysema, respectively. COPD survival was 90.9% (95% CI: 89.6, 92.2) among those with emphysema and 97.7% (95% CI: 97.3, 98.1) among those without emphysema. COPD survival was 94.2%, 85.1%, and 70.3% for mild, moderate, and severe emphysema, respectively. CVD survival was 81.4% (95% CI: 79.7, 83.1) among those with emphysema and 85.8% (95% CI: 84.9, 86.8) among those without emphysema. CVD survival was 81.8%, 81.1%, and 79.1% for mild, moderate, and severe emphysema, respectively.

Multivariable Analyses

Multivariable Cox regression analyses, adjusting for sex, age, pack-years of smoking, and years since quitting, are shown in Table 3 for all causes of death, COPD deaths, and CVD deaths. First, for all causes of death, the presence of emphysema was associated with increased all causes of death (model 1: unadjusted HR, 1.60; $P < .001$). After adjusting for sex, age, pack-years of smoking, and years since quitting, the association remained but was attenuated (model 4: adjusted HR, 1.29; $P < .001$). When evaluating the effect of extent of emphysema, results suggested a dose-response relationship, with the risk of all-cause deaths increasing with increasing extent of emphysema compared with participants without emphysema; the adjusted HRs were 1.15 ($P < .001$) for mild, 1.54 ($P < .001$) for moderate, and 2.28 ($P < .001$) for severe emphysema (model 5, Table 3).

For COPD deaths (Table 3), emphysema was associated with a higher risk (model 1: unadjusted HR, 4.52; $P < .001$) than for all causes of death and remained after adjustment (model 4: adjusted HR, 3.29; $P < .001$). A dose-response relationship was observed, with adjusted HRs of 2.07 ($P < .001$) for mild, 5.31 ($P < .001$) for moderate, and 12.06 ($P < .001$) for severe emphysema (model 5). Considering competing causes of non-COPD deaths using the Fine-Gray subdistribution hazard model, the association between emphysema and COPD deaths remained but was attenuated (unadjusted HR, 4.04; $P < .001$; adjusted HR, 3.06; $P < .001$).

The cumulative incidence function curves from the Fine-Gray model, depicting the association between emphysema severity and COPD death, are shown in Figure 5. Greater emphysema severity was linked to a higher cumulative incidence of COPD death, with the highest risk in severe cases, followed by moderate and mild, and the lowest in those without emphysema.

For CVD deaths (Table 3), emphysema was associated with increased risk of CVD death in the unadjusted model (model 1: unadjusted HR, 1.38; $P < .001$) and remained after adjustment (model 4: adjusted HR, 1.14; $P = .04$). However, there was no longer evidence of an association between CVD deaths and emphysema severity (model 5, Table 3). In the competing risk analysis, the association was attenuated (unadjusted model 1: HR, 1.22; $P = .001$), and there was no evidence of an association after adjusting for sex and age (model 2, Table 3). There was also no evidence of an association between emphysema severity and CVD deaths using the Fine-Gray model.

Discussion

Long-term studies evaluating the impact of emphysema are limited. We therefore analyzed 25-year mortality in a prospective lung cancer screening cohort of 9047 asymptomatic adults who currently smoke or formerly smoked and who underwent baseline low-dose chest CT in the state of New York between 2000

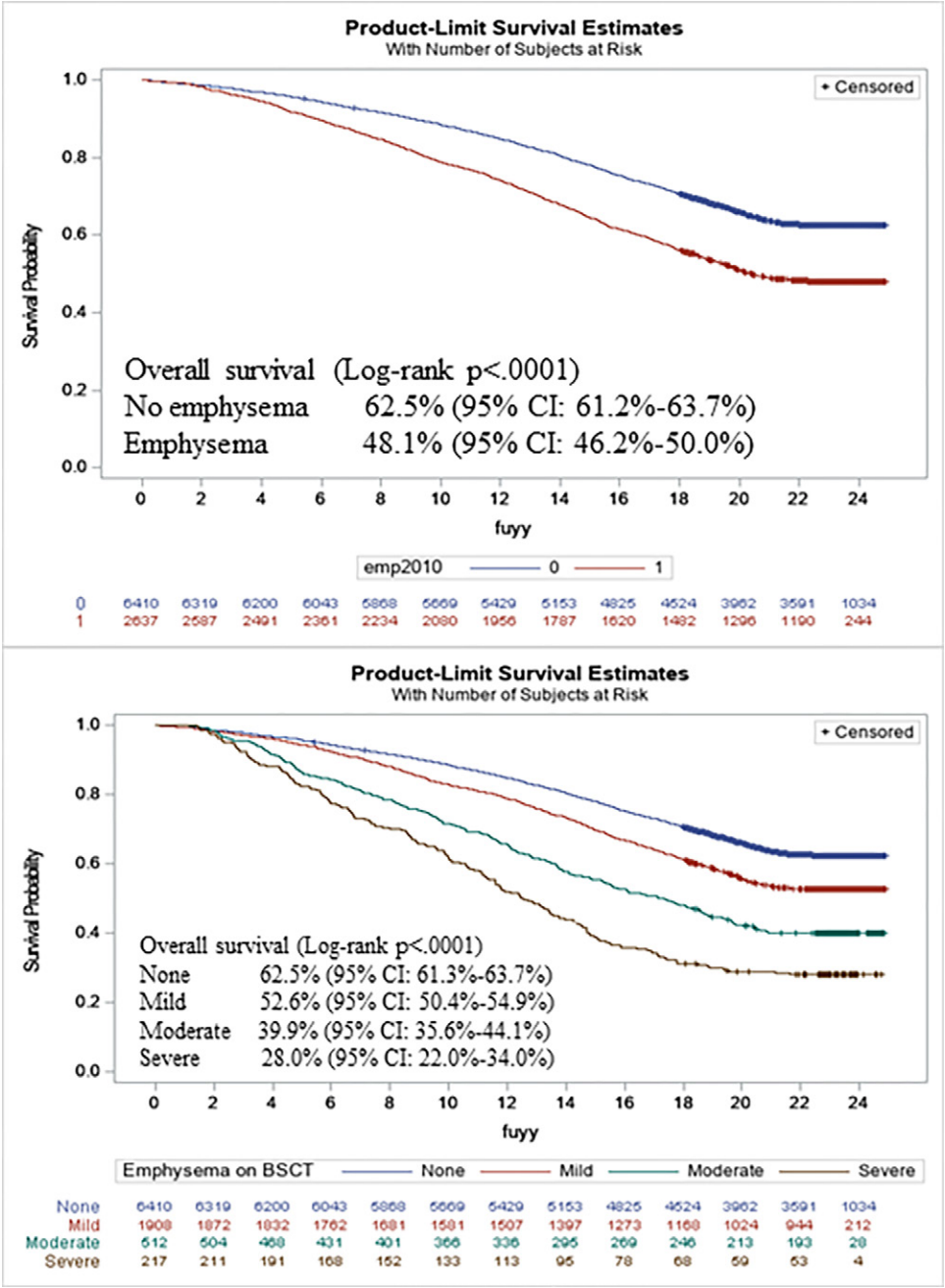

Figure 2: Kaplan-Meier curves show all-cause survival for those with emphysema versus those without (top) and stratified by emphysema categories (bottom) for 9047 baseline screening participants. Participants were categorized as having no emphysema or mild, moderate, or severe emphysema. When present, emphysema was mild if no distinct regions of reduced attenuation were visible on the CT scan, but vascular splaying indicates parenchymal expansion, or if only occasional discrete low-attenuation regions were observed. Moderate emphysema was defined by the presence of identifiable low-attenuation regions affecting less than half of the lung parenchyma, whereas severe emphysema was defined by the presence of identifiable low-attenuation regions involving more than half of the lung parenchyma. A scoring system from 0 to 3 was applied, corresponding to none, mild, moderate, and severe emphysema, respectively. BSCT = baseline CT scan.

and 2008 (4). By December 31, 2024, 3738 of 9047 participants (41.3%) had died, most commonly from cardiovascular disease (CVD) (n = 1153; 12.7%), followed by chronic obstructive pulmonary disease (COPD) (n = 295; 3.3%). This extended follow-up underscores the value of reporting baseline emphysema scores. After adjusting for sex, age, pack-years, and years since quitting, a single visual emphysema score remained an independent predictor of all-cause (hazard ratio [HR], 1.29; P < .001), COPD (HR, 3.29; P < .001), and CVD (HR, 1.14; P = .04) deaths.

Emphysema, as an imaging marker of long-term mortality, has been studied using visual or quantitative assessments (12–18). Our study stands out for its long follow-up and comprehensive analysis of causes and competing causes of death in a large lung cancer screening cohort. Consistent with previous research, our findings show an increased risk of all causes of death by emphysema presence and by its severity, ranging from a 1.15-fold increase in mild emphysema to a 2.28-fold increase in severe emphysema.

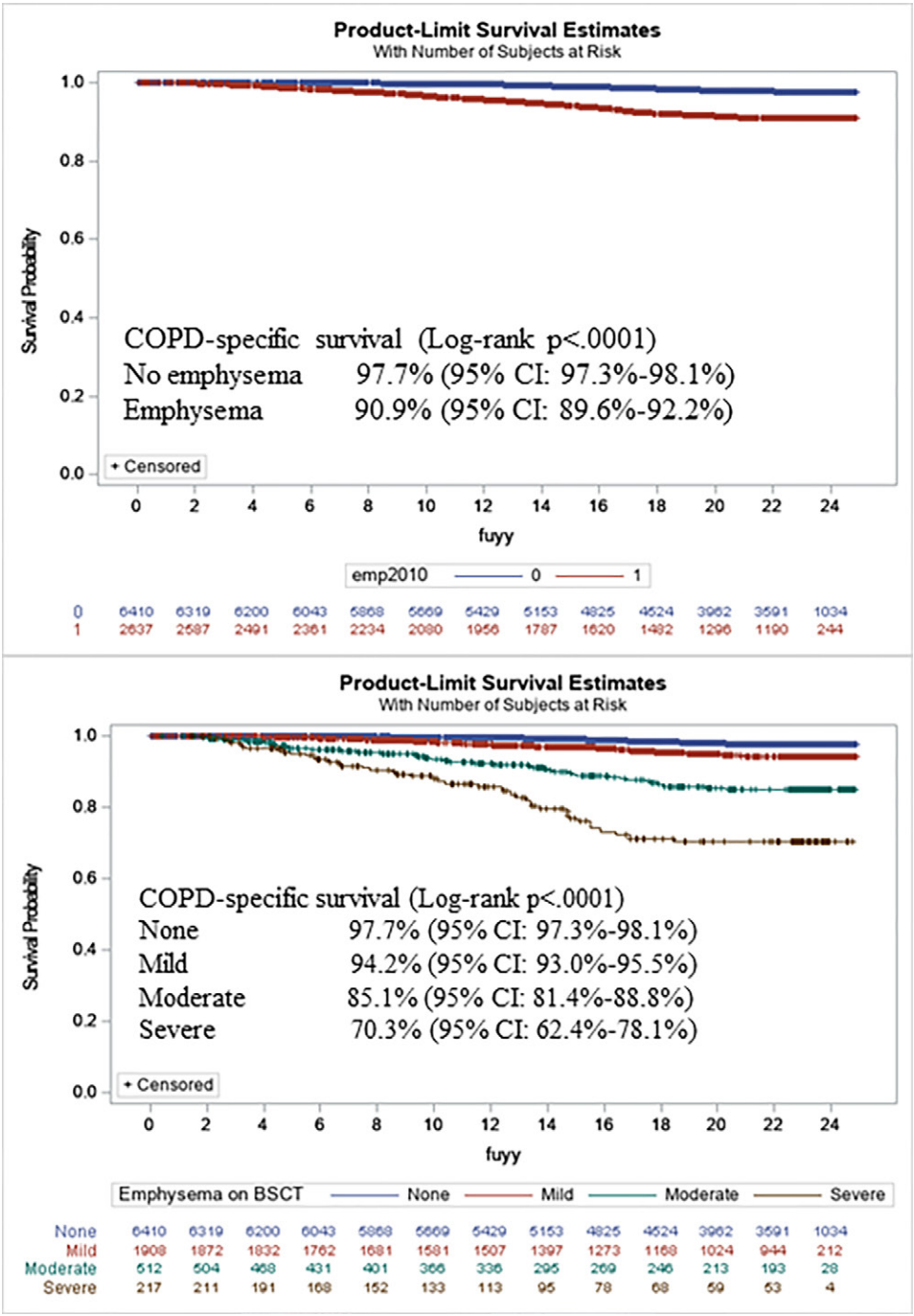

Figure 3: Kaplan-Meier curves show chronic obstructive pulmonary disease (COPD)-specific survival for those with emphysema versus those without (top) and when stratified by emphysema categories (bottom) for 9047 baseline screening participants. Participants were categorized as having no emphysema or mild, moderate, or severe emphysema. When present, emphysema was mild if no distinct regions of reduced attenuation were visible on the CT scan, but vascular splaying indicates parenchymal expansion, or if only occasional discrete low-attenuation regions were observed. Moderate emphysema was defined by the presence of identifiable low-attenuation regions affecting less than half of the lung parenchyma, whereas severe emphysema was defined by the presence of identifiable low-attenuation regions involving more than half of the lung parenchyma. A scoring system from 0 to 3 was applied, corresponding to none, mild, moderate, and severe emphysema, respectively. BSCT = baseline CT scan.

Three studies with median follow-up of 5, 8, and 12 years (13,16,18) analyzed causes of death, all using quantitative emphysema measurements. The strongest association was observed between emphysema and respiratory or COPD-related deaths, with emphysema outperforming the Global Initiative for Chronic Obstructive Lung Disease (or GOLD), classification as a predictor (16). A 10-fold risk of chronic lower respiratory disease death over 12 years (13) aligns with the 10.26-fold increase seen in severe emphysema in our study. Emphysema is also associated with deaths in people without COPD (9,13), regardless of smoking, clinical disease, or airflow limitation. Emphysema with its parenchymal and vascular loss reduces the gas exchange region

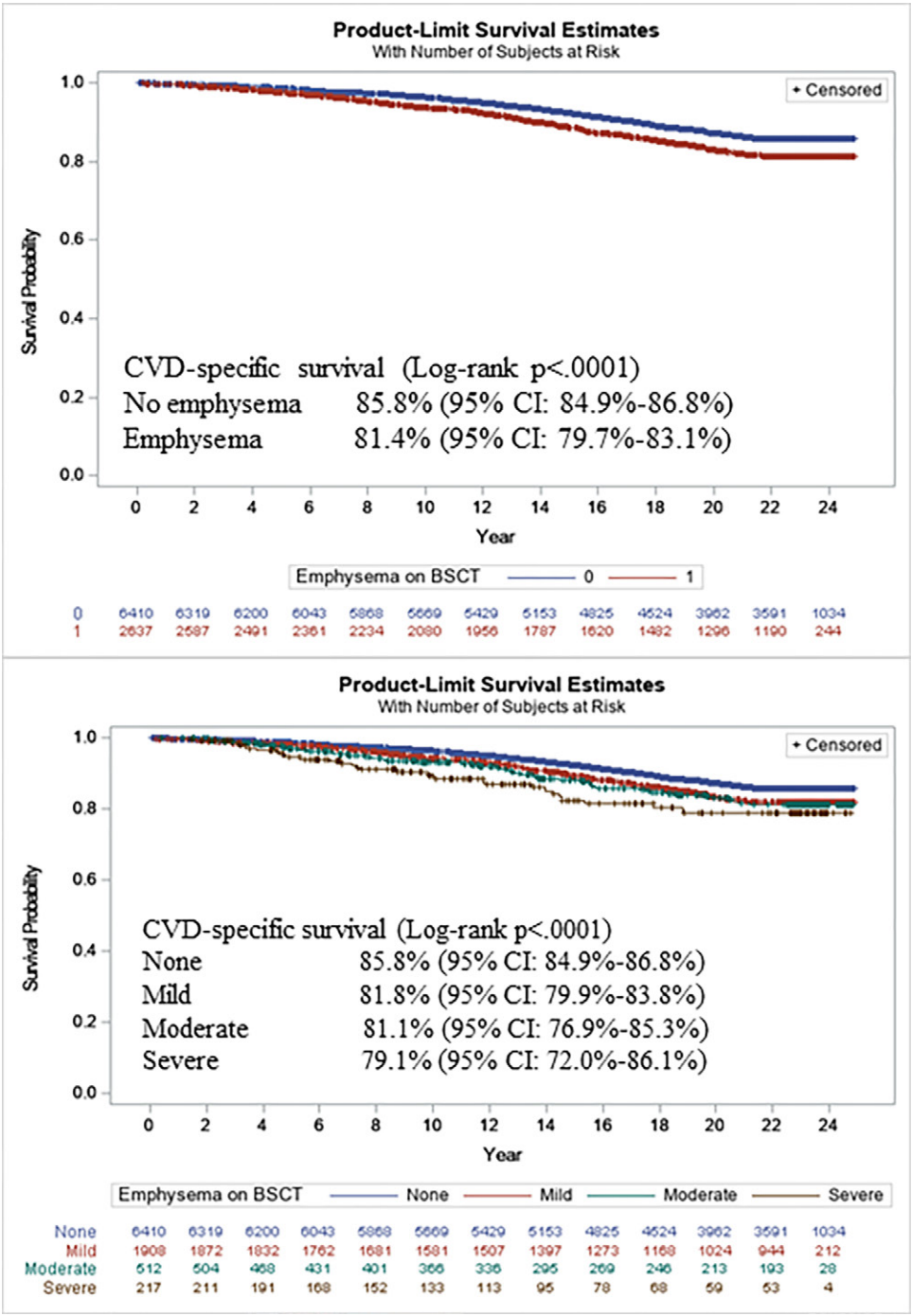

Figure 4: Kaplan-Meier curves show cardiovascular disease (CVD)-specific survival for those with emphysema versus those without (top) and when stratified by emphysema categories (bottom) for 9047 baseline screening participants. Participants were categorized as having no emphysema or mild, moderate, or severe emphysema. When present, emphysema was mild if no distinct regions of reduced attenuation were visible on the CT scan but vascular splaying indicates parenchymal expansion, or if only occasional discrete low-attenuation regions were observed. Moderate emphysema was defined by the presence of identifiable low-attenuation regions affecting less than half of the lung parenchyma, whereas severe emphysema was defined by the presence of identifiable low-attenuation regions involving more than half of the lung parenchyma. A scoring system from 0 to 3 was applied, corresponding to none, mild, moderate, and severe emphysema, respectively. BSCT = baseline CT scan.

and causes airway untethering, contributing to hypoxemia and impaired lung function (28). Furthermore, emphysema-driven systemic and lung-specific inflammation (29) may result in poor residual functional status and higher lung-related mortality.

Two long-term studies evaluated CVD deaths with conflicting results (13,16). The Multi-Ethnic Study of Atherosclerosis (MESA) (13) found no association with emphysema, whereas the Norwegian GenKOLS cohort (16) reported a 37-month shorter survival with greater emphysema severity after adjusting for potential confounders. The findings of MESA may be due to its low proportion of individuals with emphysema (7.9%), high proportion of individuals who never smoked (45.3%), and exclusion of participants with known CVD, whereas the GenKOLS study included only participants who smoked. Additionally, MESA

Table 3: Multivariable Cox Proportional Hazard Model and Fine-Gray Subdistribution Hazard Model for All-Cause, COPD, and CVD Deaths according to Baseline Emphysema Categories

	All-Cause Death		COPD Death				CVD Death			
	Cox Proportional Hazard Model		Cox Proportional Hazard Model		Subdistribution Hazard Model		Cox Proportional Hazard Model		Subdistribution Hazard Model	
Variable	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value	Hazard Ratio	*P* Value
Emphysema alone (model 1)	1.60 (1.50, 1.71)	<.001	4.52 (3.56, 5.71)	<.001	4.04 (3.20, 5.11)	<.001	1.38 (1.22, 1.56)	<.001	1.22 (1.08, 1.38)	.001
Emphysema										
Adjusted for sex and age (model 2)	1.47 (1.37, 1.57)	<.001	4.14 (3.27, 5.23)	<.001	3.76 (2.97, 4.76)	<.001	1.25 (1.11, 1.41)	.0004	1.10 (0.97, 1.25)	.14
Adjusted for sex, age, and smoking status (model 3)	1.35 (1.26, 1.44)	<.001	3.58 (2.82, 4.54)	<.001	3.30 (2.59, 4.21)	<.001	1.17 (1.03, 1.33)	.01	1.05 (0.93, 1.20)	.43
Adjusted for sex, age, smoking status, and smoking quit time (model 4)	1.29 (1.21, 1.38)	<.001	3.29 (2.59, 4.18)	<.001	3.06 (2.40, 3.90)	<.001	1.14 (1.01, 1.29)	.04	1.04 (0.91, 1.18)	.59
According to emphysema extent (model 5)*										
None	Reference	…	Reference	…	Reference	…	Reference	…	Reference	…
Mild	1.15 (1.06, 1.24)	<.001	2.07 (1.56, 2.76)	<.001	2.01 (1.51, 2.68)	<.001	1.13 (0.99, 1.30)	.08	1.11 (0.96, 1.28)	.15
Moderate	1.54 (1.36, 1.74)	<.001	5.31 (3.82, 7.38)	<.001	4.57 (3.26, 6.42)	<.001	1.07 (0.84, 1.38)	.58	0.87 (0.67, 1.12)	.28
Severe	2.28 (1.94, 2.69)	<.001	12.06 (8.43, 17.27)	<.001	8.65 (5.88, 12.72)	<.001	1.43 (1.00, 2.05)	.053	0.87 (0.59, 1.28)	.49

Note.—Data in parentheses are 95% CIs. Participants were categorized as having no emphysema or mild, moderate, or severe emphysema. When present, emphysema was mild if no distinct regions of reduced attenuation were visible on the CT scan but vascular splaying indicates parenchymal expansion, or if only occasional discrete low-attenuation regions were observed. Moderate emphysema was defined by the presence of identifiable low-attenuation regions affecting less than half of the lung parenchyma, whereas severe emphysema was defined by the presence of identifiable low-attenuation regions involving more than half of the lung parenchyma. A scoring system from 0 to 3 was applied, corresponding to none, mild, moderate, and severe emphysema, respectively. COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease.

* Model 5 adjusted for sex, age, smoking status, and smoking quit time.

cohort found no link between emphysema and CAC, whereas our study showed an increase in non-zero CAC scores with greater emphysema severity ($P < .001$).

In our study, emphysema was associated with increased CVD death, but the effect was attenuated after adjusting for sex, age, and smoking history. In the multivariable Cox model, emphysema was linked to a 14% higher risk of CVD death. However, in the Fine-Gray analysis, there was no longer any evidence of an association, suggesting that the relationship between emphysema and CVD is complex and potentially influenced by shared risk factors and the multifactorial nature of CVD. Unlike COPD deaths, where a strong dose-response relationship between emphysema severity and COPD death was observed, no significant relationship was observed between emphysema severity and CVD deaths. Our findings suggest that although emphysema is associated with an increased risk of CVD mortality in Cox models, this association is not observed in competing-risks analyses. This may indicate that COPD-related deaths overshadow the impact of emphysema on CVD mortality, as individuals with emphysema may die of COPD before experiencing CVD events. The association between emphysema and CVD has been investigated in other lung cancer screening cohorts (30,31). However, these studies assessed emphysema using software-based quantification, employing different methodologies and tools. Notably, one cohort (30) included a large number of participants (n = 15 000) but had limited follow-up (median follow-up, 6.5 years), whereas the other (31) had extended follow-up (median follow-up, 13.6 years) but a smaller sample size (n = 524). Furthermore, our cohort includes a greater number of CVD events (1153 deaths) than those two cohorts combined (635 [30] and 15 [31],

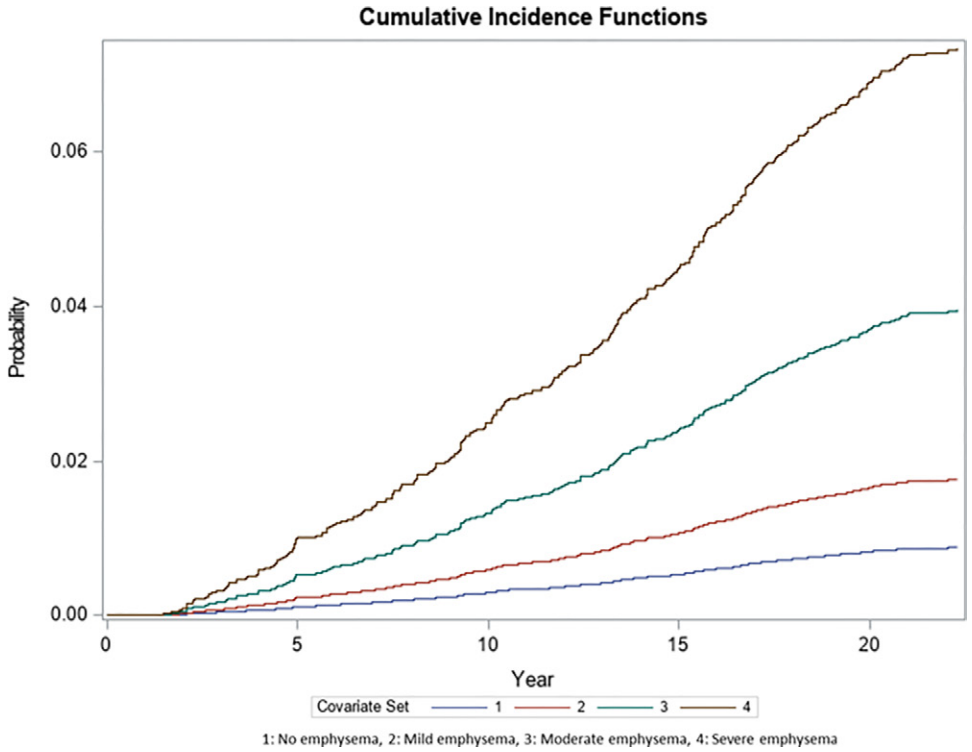

Figure 5: Cumulative incidence function curves depict the association between emphysema severity and chronic obstructive pulmonary disease mortality (adjusted for sex, age, pack-years, and quit year), accounting for competing causes of death.

respectively). Despite these differences, their findings consistently support a potential association between emphysema and CVD. Emphysema is linked to impaired left ventricular filling, reduced stroke volume, and lower cardiac output despite preserved ejection fraction (32). Hyperinflation (33) worsens pulmonary vascular resistance, reduces venous return (cardiac preload) (34), and decreases cardiac chamber size (35,36). Notably, lung volume reduction using endobronchial valves improves cardiac preload, contractility, and cardiac output by relieving hyperinflation (37).

Clinically, these findings suggest emphysema is not merely an incidental CT finding but a distinct disease entity associated with worse outcomes and increased mortality, not only from lung cancer but also from respiratory and CVD deaths. A comprehensive lung cancer screening program should also assess COPD and CVD risk to identify individuals who may benefit from targeted interventions and vigilant cardiovascular prevention to improve outcomes (38). Ongoing developments in emphysema quantification techniques and the integration of artificial intelligence methods are expected to enhance this important endeavor.

Our study has several limitations. First, although visual assessment of emphysema can be subjective, the scoring system was developed by expert consensus across the state of New York before the screening program began in 1992 and thus predates the 2015 Fleischner classification. Retrospective application of more detailed systems was not feasible, but prior studies show broad agreement between this approach and Fleischner-based assessments (2). Second, scan parameters varied over the 25-year enrollment period as imaging technology evolved. Third, we did not use automated emphysema quantification or artificial intelligence tools, which, despite being objective, have recognized limitations, including variability in acquisition and/or reconstruction, noise sensitivity, and lack of standardization, especially in multicenter studies. Notably, some studies suggest that only visually assessed emphysema correlates with long-term functional decline (39). Fourth, changes in smoking, comorbidities, or treatments over time were not captured, possibly biasing risk estimates. Fifth, residual confounding may remain despite adjustment for key variables. Lastly, although the National Death Index is a robust source, some COPD and CVD deaths may have been misclassified.

In conclusion, emphysema on a baseline low-dose CT scan was a robust predictor of all-cause mortality, as well as mortality from major comorbidities such as chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD), as shown by the 25-year follow-up in a lung cancer screening cohort. These findings highlight the clinical relevance of CT-diagnosed emphysema and its potential role in prompting earlier preventive measures for major causes of death. Given that both emphysema and coronary artery calcification stem from smoking, future research on their progression may provide further insights into their interplay and refine CVD and COPD risk stratification.

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