Association between Chest CT–defined Emphysema and Lung Cancer: A Systematic Review and Meta-Analysis

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Conflicts of interest are listed at the end of this article.

To perform a systematic review and meta-analysis of the association between chest CT–defined emphysema and the presence of lung cancer.

Materials and Methods: The PubMed, Embase, and Cochrane databases were searched up to July 15, 2021, to identify studies on the association between emphysema assessed visually or quantitatively with CT and lung cancer. Associations were determined by emphysema severity (trace, mild, or moderate to severe, assessed visually and quantitatively) and subtype (centrilobular and paraseptal, assessed visually). Overall and stratified pooled odds ratios (ORs) with their 95% CIs were obtained.

Results: Of the 3343 screened studies, 21 studies (107082 patients) with 26 subsets were included. The overall pooled ORs for lung cancer given the presence of emphysema were 2.3 (95% CI: 2.0, 2.6; F = 35%; 19 subsets) and 1.02 (95% CI: 1.01, 1.02; six subsets) per 1% increase in low attenuation area. Studies with visual (pooled OR, 2.3; 95% CI: 1.9, 2.6; F = 48%; 12 subsets) and quantitative (pooled OR, 2.2; 95% CI: 1.8, 2.8; F = 3.7%; eight subsets) assessments yielded comparable results for the dichotomous assessment. Based on six studies (1716 patients), the pooled ORs for lung cancer increased with emphysema severity and were higher for visual assessment (2.5, 3.7, and 4.5 for trace, mild, and moderate to severe, respectively) than for quantitative assessment (1.9, 2.2, and 2.5) based on point estimates. Compared with no emphysema, only centrilobular emphysema (three studies) was associated with lung cancer (pooled OR, 2.2; 95% CI: 1.5, 3.2; P < .001).

Conclusion: Both visual and quantitative CT assessments of emphysema were associated with a higher odds of lung cancer, which also increased with emphysema severity. Regarding subtype, only centrilobular emphysema was significantly associated with lung cancer.

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Lung cancer is the primary cause of cancer-related death worldwide (1), with more than 1 million attributable deaths each year since 2000 (2). However, lung cancer risk can be reduced by identifying treatable risk factors, such as chronic lung inflammation (3), together with smoking, genetics, diet, and occupational exposure (3). Emphysema is characterized pathologically by the presence of diffuse chronic inflammation of the lung parenchyma, oxidative stress, and lung destruction (4). Thus, lung cancer and emphysema are linked by common predisposing risk factors and multiple molecular inflammatory processes (5).

Emphysema can be assessed with use of chest CT, radiography, or pulmonary function tests, although chest CT has the highest sensitivity (6,7) and is considered the reference standard for noninvasive assessment (8). Numerous studies have explored the association between the chest CT assessment of emphysema and lung cancer, but they have yielded inconsistent results (9–12). Associations have been shown between emphysema and lung cancer on chest CT scans for qualitative visual assessment by radiologists (12,13), but not for automated quantitative assessment (9,10). These data were subsequently confirmed by comparing the two methods directly (14), indicating that the method used to assess emphysema may have affected previous outcomes. Consistent with this, a meta-analysis in 2012 showed that visual assessment of emphysema at chest CT was independently associated with lung cancer (15), but no such association was present for quantitative assessment. However, that conclusion was based on data from only two studies. Although systematic reviews in 2020 and 2016 concluded that emphysema assessed with chest CT was associated with an increased risk of lung cancer (16,17), they did not provide pooled risk estimates or stratify data by how
Both visual and quantitative emphysema assessed at chest CT were associated with a higher odds ratio of lung cancer, and this association increased with emphysema severity.

Key Points
- Systematic review of 21 studies (107,082 patients) comparing the association of chest CT–defined emphysema with lung cancer showed an overall pooled odds ratio (OR) of 2.3 ($P < .001$).
- ORs for lung cancer increased with emphysema severity and were higher for visual assessment (OR: 2.5, 3.7, and 4.5 for trace, mild, and moderate to severe emphysema, respectively) compared with quantitative assessment (OR: 1.9, 2.2, and 2.5, respectively).

Materials and Methods

Search Strategy and Study Selection
This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines (22) and registered in the international prospective register of systematic reviews, or PROSPERO (no. CRD42021262163). The published studies were retrieved and screened from the PubMed, Embase, and Cochrane databases from inception to July 15, 2021 (Table E1 [online]).

We included studies investigating the association between emphysema and lung cancer if they were original research and published in English, with lung cancer diagnosed at histopathologic examination (independent of histologic subtype) and emphysema diagnosed at CT. The exclusion criteria of studies are specifically described in Figure 1. For multiple articles concerning the same cohort, we selected the study from which most data could be extracted.

Definitions of Emphysema and Lung Cancer
Visual emphysema was defined as disrupted lung vasculature and parenchyma with low attenuation occupying any lung zone (at least trace) at chest CT, as evaluated by radiologists using the National Emphysema Treatment Trial (ie, NETT) or Fleischner Society (23,24) guidelines or comparable (Table E2 [online]). Quantitative emphysema was defined by the percentage of total lung volume below a given Hounsfield unit (HU) threshold ($950$ HU at full inspiration), reported as the low attenuation area percentage (LAA%). A specific LAA% threshold was defined “emphysema present.” In the grading of emphysema severity (trace, mild, moderate, and severe), specific percentages of visual (Fleischner Society or NETT) or quantitation were used to assess emphysematous lung tissue destruction at CT (ie, mild: 0%–25%, moderate: 26%–50%, and severe: ≥51%). The main emphysema subtypes were paraseptal and centrilobular, which could only be assessed visually at CT. Paraseptal emphysema was defined as the presence of a few well-demarcated, round, juxtapleural lucencies, while centrilobular emphysema was defined as centrilobular distribution of lucencies. Finally, eligible cases of lung cancer were confirmed pathologically from surgical, biopsy, or cytologic samples, without specification of the subtype.

Statistical Analysis
We stratified studies by visual or quantitative assessment and set confirmed lung cancer as the main outcome. The adjusted OR given the presence of emphysema was the main outcome, with risk ratios and hazard ratios interpreted as ORs due to the low incidence of lung cancer (27,28). When a study reported stratified ORs, an overall OR was estimated by applying a random-effect model. For studies that stratified ORs by severity, we pooled data for moderate and severe emphysema. To estimate the odds of lung cancer developing among patients with and without emphysema, we pooled data under the assumption of homogeneity by applying a random-effect model. Forest plots are presented to illustrate the pooled results and related heterogeneity. Pooled ORs and 95% CIs are provided for dichotomous or continuous measurements of emphysema. Analyses were repeated for emphysema severity and subtype (visual assessment).
Heterogeneity was estimated with use of the $I^2$ statistic and quantified as low (0%–25%), moderate (26%–50%), substantial (51%–75%), or considerable (76%–100%) (29,30). Potential sources of heterogeneity were explored with stratified analysis based on participant sources, study design, effect size study quality, CT section thickness (normal [≥5 mm] vs thin [0.5–1.25 mm]), and HU cutoff value. Funnel plots were used to evaluate publication bias. Asymmetry, which is an indication for publication bias, was evaluated visually and with the Egger test. As the next step, the trim-and-fill method was applied to evaluate the stability of our results by correcting for publication bias. The robustness of estimates was evaluated by leave-one-out sensitivity analysis, removing each study sequentially and recalculating the OR.

Statistical analysis was conducted with Stata Standard Edition, version 15.1 (StataCorp); $P < .05$ was considered indicative of statistically significant difference.

## Results

### Study Selection and Quality

As shown in Figure 1, 3217 of 3270 studies were excluded after screening abstract and title. Full-text screening resulted in 21 articles that met all criteria for inclusion in the meta-analysis. The $k$ values of the two screening stages were 0.80 (title and abstract) and 0.62 (full text), respectively. Of the included studies, two featured both visual and quantitative assessment (31,32), 20 reported emphysema as a dichotomous variable only (visual and quantitative assessment), two as a continuous variable only (33,34), and four as both variables (9,10,19,31). This resulted in 26 study subsets for inclusion in the final meta-analysis. Regarding study quality, 15, six, and none were considered high, medium, and low quality, respectively (Table E3 [online]).

### Study Characteristics

Overall, the 21 studies included 3907 patients with lung cancer and 103 175 controls (Tables 1, 2), with sample sizes ranging from 120 to 62 124. By study design, cohort studies (52% [11 of 21 studies]) contributed 1868 cases of lung cancer from 101 679 patients, and case-control studies (48% [10 of 21]) contributed 2039 cases of lung cancer from 5403 patients. In total, 74% of the 107 082 patients came from North America (78 874 [11 studies]), 26% from Europe (27 392 [eight studies]), and 0.8% from Asia (816 [two studies]).

Visual assessment was used in 12 study subsets with 95 062 patients, while quantitative dichotomous assessment was used in eight study subsets with 4758 patients, identifying emphysema in 25% (23 742 of 95 062) and 27% (1079 of 4046), respectively. Moreover, quantitative continuous assessment (ie, LAA%) was used in six subsets with 10 014 patients. The definitions of emphysema used for visual and quantitative assessment varied across studies (Table E2 [online]). The HU threshold for low attenuation area in quantitative assessments varied from −880 to −950 HU, while LAA% cutoffs for the presence of emphysema varied from 1% to 25%. This contributed to a wide variation in the incidence of emphysema, from 8% (44 of 558 patients) to 80% (195 of 243 patients). Moreover, uniformity was lacking for both HU thresholds and LAA% cutoffs for emphysema severity.

All studies confirmed lung cancer with histologic examination. A total of six studies (three visual, three quantitative; 459 lung cancers among 6242 patients) explored the relationship between emphysema severity and lung cancer, whereas three studies (all visual; 380 lung cancers among 1716 patients) explored the association between emphysema subtype and lung cancer. Participant sources were hospital-based (33% [seven of 21 studies]) or population-based (67% [14 of 21]).

### Data Synthesis and Meta-Analysis

The overall pooled estimate for the association between emphysema and lung cancer was 2.3 (95% CI: 2.0, 2.6) (Fig 2), which was robust in the leave-one-out sensitivity analysis (Fig E1 [online]). The pooled OR for every 1% increase in the LAA% was 1.02 (95% CI: 1.01, 1.02) (Fig E2 [online]).

![Figure 1: Flowchart of study selection.](image-url)
Moderate heterogeneity was observed among studies \((I^2 = 34.6\% ; P = .07)\), reasonable symmetry was identified at the visual inspection of funnel plot (Fig E3 [online]), and the Egger test helped identify evidence of potential publication bias \((P = .04)\) favoring the existence of unpublished studies. Thus, the trim-and-fill correction for potential publication bias did not alter the association \((pooled OR, 2.0; 95\% CI: 1.7, 2.3)\) (Fig E4 [online]).

### Association between Emphysema and Lung Cancer

The pooled OR for lung cancer given emphysema was 2.3 (95\% CI: 1.9, 2.6) in studies using visual assessment and 2.2 (95\% CI: 1.8, 2.8) in studies using quantitative dichotomous assessment (Fig 3). Low heterogeneity \((I^2 = 3.7\% ; P = .40)\) was observed in studies using quantitative assessment, and moderate heterogeneity \((I^2 = 48.4\% ; P = .03)\) was observed in studies using visual assessment (Table 3).

### Association between Emphysema Severity and Lung Cancer

Independent associations existed between different emphysema severities and lung cancer (Fig 4), with the overall pooled ORs for lung cancer gradually increasing (2.2, 3.2, and 3.6) as the emphysema severity increased (trace, mild, and moderate to severe, respectively) (Table 4). Substantial heterogeneity was observed for studies that reported moderate to severe emphysema \((I^2 = 52.6\% )\) compared with trace \((I^2 = 0\% )\) and mild \((I^2 = 20.7\% )\) emphysema. The three studies that used visual assessment gave pooled ORs of 2.5, 3.7, and 4.5 for trace, mild, and moderate to severe emphysema, respectively; by contrast, the three studies that used quantitative assessment produced corresponding pooled ORs of 1.9, 2.2, and 2.5.

### Association between Visual Emphysema Subtypes and Lung Cancer

The pooled OR for lung cancer odds in the presence of centrilobular emphysema was 2.2 (95\% CI: 1.5, 3.2), with no heterogeneity observed across the three relevant studies \((I^2 = 0\% )\). However, we found no evidence of an association between paraseptal emphysema and lung cancer \((pooled OR, 1.1; 95\% CI: 0.6, 2.0)\) (Table 5), and there was high heterogeneity \((I^2 = 65.6\% )\) (Fig 5) in this subset.

### Sources of Heterogeneity

In the additional stratified analyses, the potential reasons for heterogeneity were explored (Table E6 [online]), but we could not find any explanation. The pooled ORs were comparable between case-control (2.2; 95\% CI: 1.8, 2.8; \(I^2 = 55.0\% )\) and cohort (2.3; 95\% CI: 2.0, 2.7; \(I^2 = 0\% )\) stud-
ies (P = .46). Population-based studies, which had moderate heterogeneity (I² = 27.0%), had a comparable pooled OR (2.2; 95% CI: 1.9, 2.5) to that of hospital-based studies (2.6; 95% CI: 1.9, 3.6; I² = 32.7% [P = .06]). The variation in study characteristics and study quality did not affect our results (Table E6 [online]). The pooled effect sizes were comparable between studies that reported hazard ratios (2.3; 95% CI: 1.9, 2.8; I² = 19.3%) and those that reported ORs (2.3; 95% CI: 1.9, 3.6; I² = 47.6% [P = .64]). Emphysema assessed quantitatively based on thin CT sections was associated with lung cancer (pooled OR, 2.2; 95% CI: 1.3, 3.7; P = .002), while this was not the case for the assessment based on normal section thickness. Similarly for LAA HU thresholds, an association with lung cancer was found based on a cutoff of −950 HU (pooled OR, 2.6; 95% CI: 2.0, 3.4; P < .001), but not for −900 HU.

### Discussion

In this systematic review and meta-analysis comparing the association of emphysema at chest CT with the presence of lung cancer, we found that both the visual and quantitative CT assessments of emphysema were associated with a higher risk of lung cancer (pooled OR, 2.3; 95% CI: 1.9, 2.6; P < .001), and the odds increased with emphysema severity. Regarding subtype, only centrilobular emphysema was associated with lung cancer (pooled OR, 2.2; 95% CI: 1.5, 3.2; P < .001).

Our study showed that emphysema at CT was associated with a 2.3-fold increased odds of lung cancer, comparable to that reported by Brenner et al (35) and Zhang et al (36). However, Smith et al (15) only found this association for visually diagnosed emphysema, whereas our study demonstrated it for both visual and quantitative methods, irrespective of whether emphysema was analyzed as a dichotomous or continuous variable. An

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**Table 2: Characteristics of Included Studies That Assessed Emphysema Quantitatively at Chest CT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>With and without Lung Cancer*</th>
<th>Age (y)†</th>
<th>Source</th>
<th>Study Design</th>
<th>Effect Size‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kishi et al 2002 (10)</td>
<td>U.S.</td>
<td>24</td>
<td>96</td>
<td>HB</td>
<td>Case-control; retrospective study</td>
<td>OR: 1.1 (0.5, 2.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case: 64 ± 7</td>
<td>Control: 63 ± 6</td>
<td></td>
<td></td>
<td>OR: 1.0 (0.6, 1.9)</td>
</tr>
<tr>
<td>Maldonado et al 2010 (9,48)</td>
<td>U.S.</td>
<td>64</td>
<td>377</td>
<td>PB</td>
<td>Case-control; prospective study</td>
<td>OR: 1.9 (1.1, 3.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case: 63 ± 7</td>
<td>Control: 62 ± 6</td>
<td></td>
<td></td>
<td>OR: 1.04 (0.8, 1.3)</td>
</tr>
<tr>
<td>Gierada et al 2011 (11)</td>
<td>U.S.</td>
<td>279</td>
<td>279</td>
<td>PB</td>
<td>Case-control; retrospective study</td>
<td>OR: 2.0 (1.0, 3.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall: 59 ± 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aamli Gagnant et al 2017 (19)</td>
<td>Norway</td>
<td>34</td>
<td>741</td>
<td>PB</td>
<td>Cohort; prospective study</td>
<td>HR: 2.4 (0.9, 6.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR: 1.03 (0.7, 1.5)</td>
</tr>
<tr>
<td>Chubachi et al 2017 (18)</td>
<td>Japan</td>
<td>21</td>
<td>219</td>
<td>HB</td>
<td>Cohort; prospective study</td>
<td>OR: 4.2 (1.0, 29.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case: 73 ± 7</td>
<td>Control: 73 ± 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouronte-Roitbás et al 2018 (20)</td>
<td>Spain</td>
<td>169</td>
<td>74</td>
<td>HB</td>
<td>Case-control; retrospective study</td>
<td>OR: 2.2 (1.1, 4.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case: 69 ± 9</td>
<td>Control: 65 ± 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nishio et al 2019 (34)</td>
<td>Japan</td>
<td>283</td>
<td>293</td>
<td>HB</td>
<td>Case-control; retrospective study</td>
<td>OR: 1.01 (1.00, 1.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case: 69 ± 10</td>
<td>Control: 65 ± 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Husebø et al 2019 (49)</td>
<td>Norway</td>
<td>31</td>
<td>681</td>
<td>HB</td>
<td>Cohort; prospective study</td>
<td>HR: 4.4 (1.7, 10.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case: 64 ± 7</td>
<td>Overall: 58 ± 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labaki et al 2021 (33)</td>
<td>U.S.</td>
<td>353</td>
<td>6909</td>
<td>PB</td>
<td>Cohort; prospective study</td>
<td>HR: 1.02 (1.01, 1.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overall: 62 ± 5</td>
<td></td>
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</tr>
<tr>
<td>Schwartz et al 2016 (32)</td>
<td>U.S.</td>
<td>341</td>
<td>752</td>
<td>PB</td>
<td>Case-control; retrospective study</td>
<td>OR (visual): 1.8 (1.4, 2.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case: 64 ± 10</td>
<td>Control: 62 ± 9</td>
<td></td>
<td></td>
<td>OR (quantitative): 2.7 (1.8, 4.0)</td>
</tr>
<tr>
<td>Carr et al 2018 (31)</td>
<td>U.S.</td>
<td>169</td>
<td>671</td>
<td>PB</td>
<td>Case-control; prospective study</td>
<td>OR (visual): 2.3 (1.4, 3.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case: 66 ± 8</td>
<td>Control: 64 ± 8</td>
<td></td>
<td></td>
<td>OR (quantitative): 1.03 (0.6, 1.8)</td>
</tr>
</tbody>
</table>

Note.—See Table E5 (online) for full details. HB = hospital-based, HR = hazard ratio, OR = odds ratio, PB = population-based.

* Data are numbers of patients.
† Data are means ± SDs.
‡ Data in parentheses are 95% CIs.
§ Effect size when emphysema was assessed as a continuous variable. All effect sizes are adjusted for smoking status. For specific adjusted factors, see Table E2 (online).
explanation for this difference may be that Smith et al only included two quantitative CT studies in 2012 (1549 patients), while in our analysis, 10 studies were included (12841 patients). There was no evidence showing that source of population or study design influenced the overall association between emphysema and lung cancer. Besides, in our study, we found comparable pooled ORs for visual and quantitative assessment, implying no difference between them. Nonetheless, each method of emphysema assessment has its own limitations. Visual assessment is time-consuming, subjective, and experience-dependent and has high inter- and intraobserver variability despite well-established and standardized criteria (24,27). In contrast, although quantitative assessment is objective, quick, and highly reproducible when similar devices and protocols are used, it is hampered by inconsistencies in factors like the section thickness, HU threshold (−900 HU or −950 HU), and LAA% cutoffs (1%–25%). To illustrate this, we found no evidence of an association (P = .09) between emphysema and lung cancer when emphysema was quantitatively assessed at thick-section chest CT with a cutoff value of −900 HU. Therefore, it is recommended that a thin section thickness (≤1.5 mm) and −950-HU cutoff value are used for quantitative emphysema assessment. Given that each of these factors may affect emphysema detection with the quantitative method (14), standardization is needed to ensure the precision, reliability, and robustness required for widespread use (37–39).

The presence of emphysema, irrespective of its severity, was related to the presence of lung cancer. The odds of lung cancer increased with increasing

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**Figure 2:** Forest plot of the random-effects meta-analysis for the association between emphysema (dichotomous variable) assessed visually and/or quantitatively with CT and lung cancer in 19 studies. The overall pooled odds ratio (OR) of emphysema for lung cancer was 2.3 (95% CI: 2.0, 2.6 [P < .001]). For the studies that assessed emphysema with two methods, only the ORs assessed with the main method were pooled in the overall estimates. Squares and horizontal lines represent estimates and 95% CIs, respectively, for each study part. Diamonds indicate pooled effect sizes with 95% CIs. DL = DerSimonian and Laird. * = Study reported hazard ratios. † = Study reported risk ratios.

**Figure 3:** Forest plot of the random-effects meta-analysis for the association between emphysema and lung cancer, stratified by the emphysema assessment method. The pooled odds ratios (ORs) for lung cancer given visual and quantitative dichotomous emphysema assessment were 2.3 (95% CI: 1.9, 2.6 [P < .001]) and 2.2 (95% CI: 1.8, 2.8 [P < .001]), respectively. Squares and horizontal lines represent estimates and 95% CIs, respectively, for each study part. Diamonds indicate pooled effect sizes with 95% CIs. * = Study assessed emphysema both visually and quantitatively. DL = DerSimonian and Laird.
Table 3: Association between Emphysema and Lung Cancer Stratified by Emphysema Assessment Method

<table>
<thead>
<tr>
<th>Assessment Method</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>No. of Lung Cancers</th>
<th>Pooled Odds Ratio</th>
<th>95% CI</th>
<th>P (%)</th>
<th>95% CI</th>
<th>I² (%)</th>
<th>P Value for Heterogeneity</th>
<th>P Value for Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>12</td>
<td>95,561</td>
<td>2,330</td>
<td>2.3</td>
<td>1.9, 2.6</td>
<td>48.4</td>
<td>.03</td>
<td>.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative</td>
<td>8</td>
<td>55,31</td>
<td>1,161</td>
<td>2.2</td>
<td>1.8, 2.8</td>
<td>3.7</td>
<td>.40</td>
<td></td>
<td></td>
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</tbody>
</table>

Note.—Unless otherwise specified, analysis was based on emphysema when measured as a dichotomous variable.

Figure 4: Forest plot of the random-effects meta-analysis for the association between emphysema severity (assessed visually and/or quantitatively) and lung cancer. The overall pooled odds ratios (ORs) of trace, mild, and moderate to severe emphysema for lung cancer were 2.2 (95% CI: 1.4, 3.6 [P = .001]), 3.2 (95% CI: 2.2, 4.6 [P < .001]) and 3.6 (95% CI: 2.2, 6.0 [P < .001]), respectively. Adjusted factors in these mixed-effects models varied, as shown in Table E2 (online). Squares and horizontal lines represent estimates and 95% CIs, respectively, for each study part. Diamonds indicate pooled effect sizes with 95% CIs. DL = DerSimonian and Laird.

levels of emphysema severity. We identified several studies that reported inconsistent results regarding the association between increasing emphysema severity and increasing lung cancer odds, with some suggesting that this trend existed (18,21) and others suggesting the opposite (9,31). It may be that the limited sample sizes for severe emphysema in the studies (82 and 135 patients) resulted in showing no trend. The analysis stratified by assessment method showed that ORs for lung cancer increased with increasing emphysema severity and that this association was higher for visual assessment. This is not surprising, given that visual assessment relies on subjective estimation of emphysema severity and not a prespecified HU threshold. Validated or cross-calibrated quantitative and visual assessments of severity have not previously been well established in the literature. Our cutoff values for categorizing emphysema severity were generally higher for the visual (mild, ≤10%; moderate, >10%) than for the quantitative (mild, ≤10%; moderate, >10%) assessments (9,12).

Centrilobular emphysema, but not paraseptal emphysema, was independently associated with an increased odds of lung cancer. Although these results should be interpreted cautiously due to their reliance on only three studies, the large sample of 1370 participants should increase the reliability (48% centrilobular, 34% paraseptal, 15% controls) (20,21,31). If paraseptal emphysema truly has no association with lung cancer, its presence may also explain existing discrepancies.

Our study has limitations. First, airflow obstruction is an independent risk factor for lung cancer (40), yet some included studies did not adjust for its presence (62% [13 of 21 studies]). This confounder could have affected the pooled OR for lung cancer. Second, only six studies reported the effect of emphysema severity on lung cancer, and only two reported the association for trace emphysema. Third, based on the included data in this meta-analysis, it was not possible to determine whether the presence of CT-defined emphysema leads to incremental and independent prognostic value over that of already known (shared) risk factors of emphysema and lung cancer. Finally, the cutoff value for the presence of emphysema and its severity varied among the studies, and this may likely have affected the pooled ORs.

In conclusion, emphysema diagnosed at chest CT was independently associated with a higher odds of developing lung cancer, regardless of whether it was assessed visually or quantitatively. Moreover, this risk increased with emphysema severity. Concerning visual assessment by subtype, only centrilobular emphysema was significantly associated with lung cancer. To benefit from the potential value of visual and quantitative CT assessments in early emphysema detection and lung cancer screening,
research must now establish guidelines for scanning protocols, evaluation, and nodule risk stratification.

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**Table 4: Association between Emphysema Severity and Lung Cancer**

<table>
<thead>
<tr>
<th>Emphysema Severity</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>No. of Lung Cancers</th>
<th>Pooled Odds Ratio</th>
<th>95% CI</th>
<th>F (%)</th>
<th>I² (%)</th>
<th>P Value for Heterogeneity</th>
<th>P Value for Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trace</td>
<td>3</td>
<td>747</td>
<td>34</td>
<td>2.2</td>
<td>1.4, 3.6</td>
<td>0.59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>6</td>
<td>1049</td>
<td>140</td>
<td>3.2</td>
<td>2.2, 4.6</td>
<td>20.1</td>
<td>.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>6</td>
<td>936</td>
<td>168</td>
<td>3.6</td>
<td>2.2, 6.0</td>
<td>52.6</td>
<td>.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trace</td>
<td>1</td>
<td>685</td>
<td>22</td>
<td>2.5</td>
<td>1.4, 4.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mild</td>
<td>3</td>
<td>817</td>
<td>118</td>
<td>3.7</td>
<td>2.3, 5.8</td>
<td>42.9</td>
<td>.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>3</td>
<td>637</td>
<td>124</td>
<td>4.5</td>
<td>2.5, 8.3</td>
<td>55.9</td>
<td>.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantitative*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trace</td>
<td>1</td>
<td>62</td>
<td>12</td>
<td>1.9</td>
<td>0.9, 4.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>232</td>
<td>22</td>
<td>2.2</td>
<td>1.1, 4.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>3</td>
<td>299</td>
<td>44</td>
<td>2.5</td>
<td>1.2, 5.1</td>
<td>23.0</td>
<td>.27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Cutoff value for emphysema severity varied among six studies.

**Table 5: Association between Emphysema Subtype (Visual Assessment) and Lung Cancer**

<table>
<thead>
<tr>
<th>Emphysema Subtype</th>
<th>No. of Studies</th>
<th>No. of Participants</th>
<th>No. of Lung Cancers</th>
<th>Pooled Odds Ratio</th>
<th>95% CI</th>
<th>F (%)</th>
<th>I² (%)</th>
<th>P Value for Heterogeneity</th>
<th>P Value for Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrilobular emphysema</td>
<td>3</td>
<td>660</td>
<td>258</td>
<td>2.2</td>
<td>1.5, 3.2</td>
<td>0</td>
<td>.37</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>Paraseptal emphysema</td>
<td>3</td>
<td>471</td>
<td>153</td>
<td>1.1</td>
<td>0.6, 2.0</td>
<td>65.6</td>
<td>.06</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 5:** Forest plot of the random-effects meta-analysis for the association between emphysema subtype (assessed visually only) and lung cancer. The pooled odds ratios (ORs) for lung cancer odds in the presence of centrilobular and paraseptal emphysema were 2.2 (95% CI: 1.5, 3.2 [P < .001]) and 1.1 (95% CI: 0.6, 2.0 [P = .71]). Adjusted factors in these mixed-effects models varied, as shown in Table E2 (online). Squares and horizontal lines represent estimates and 95% CIs, respectively, for each study part. Diamonds indicate effect sizes with 95% CIs. DL = DerSimonian and Laird.
Association between Chest CT–defined Emphysema and Lung Cancer

References


