The association of chest computed tomography-defined visual emphysema and prognosis in patients with nonsmall cell lung cancer

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Shareable abstract (@ERSpublications)
Computed tomography (CT)-defined emphysema is often considered a predictor of lung cancer risk. This prospective cohort study adds that CT-defined emphysema is significantly associated with worse survival, regardless of oncogene status or tumour stage. https://bit.ly/3Phnwse

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Abstract

Background Although computed tomography (CT)-defined emphysema is considered a predictor of lung cancer risk, it is not fully clear whether CT-defined emphysema is associated with the prognosis of lung cancer. We aimed to assess the clinical impact of CT-defined emphysema on the survival of lung cancer.

Methods In the prospective cohort study of nonsmall cell lung cancer (NSCLC), the correlation between CT-defined emphysema and clinical variables was analysed. A multivariable Cox regression model was built to assess the association between CT-defined emphysema and overall survival (OS) for up to 8.8 years. The differences in survival analyses were derived by Kaplan–Meier analysis and log-rank testing. Low attenuation area (LAA%) was defined as the per cent of voxels below −950 HU.

Results 854 patients were included and CT-defined emphysema was present in 300 (35.1%) at diagnosis. Epidermal growth factor receptor (EGFR) wild-type (OR 1.998; p<0.001) and anaplastic lymphoma kinase (ALK) wild-type (OR 2.277; p=0.004) were associated with CT-defined emphysema. CT-defined emphysema remained a significant predictor of prognosis adjusting for age, sex, smoking history, tumour histology and Eastern Cooperative Oncology Group Performance Status (ECOG PS), whether in I-IIIA stage (adjusted hazard ratio (HR) 1.745; p=0.017) or in IIIB-IV stage (adjusted HR 1.291; p=0.022). Stratified analyses showed that OS rate among the driver oncogene groups with different CT-defined emphysema status differed significantly (log-rank p<0.001). Furthermore, patients with centrilobular emphysema (CLE) with LAA% >17% displayed poorer survival than those with LAA% ⩽17% (median 432 *versus* 670 days; HR 1.564; p=0.020).

Conclusions CT-defined emphysema, especially CLE with LAA%>17%, is an independent predictor of NSCLC prognosis. Moreover, prospective studies are needed to further explore this association.

Introduction

Lung cancer is the leading cause of cancer-related deaths throughout the world [1], and nonsmall cell lung cancer (NSCLC) is the most frequent histological subtype (~80–85%) [2]. Numerous studies have demonstrated that computed tomography (CT)-defined emphysema is a predictor for the risk of lung cancer development [3, 4]. We questioned whether CT-defined emphysema affected the prognosis of NSCLC. Some researchers have explored the association between the prognosis of lung cancer and the presence of CT-defined emphysema but have yielded inconsistent results in different tumour stages and races [5–9]. Ueda *et al*. [10] have suggested that early-stage NSCLC patients with CT-defined emphysema, not airway

obstruction, had a poorer prognosis than those without it, while another study [8] did not find any differences in survival of lung cancer related to CT-defined emphysema among African American patients. To date, studies on the importance of CT-defined emphysema in determining the outcomes of patients with NSCLC are scarce. Moreover, molecular testing has become the standard procedure for patients with NSCLC [11, 12]. Previous studies with a comparatively small sample size indicated that the proportion of patients with CT-defined emphysema was lower in patients with epidermal growth factor receptor (EGFR) mutations than in wild-type patients [13–16]. The association between anaplastic lymphoma kinase (ALK) and CT-defined emphysema remains contradictory [14, 15]. Thus, the oncogene status of patients with CT-defined emphysema has not been thoroughly defined.

To address these issues, in this prospective cohort study, we sought to evaluate the oncogene status of NSCLC patients with CT-defined emphysema and investigate the prognostic value of CT-defined emphysema according to oncogene status and tumour stage. Other survival analyses in different stratification groups were also explored. Furthermore, we reported an exploratory analysis to assess the effects of airway obstruction on overall survival (OS).

Methods

Study population

Patients from an observational cohort with newly diagnosed NSCLC at Beijing Chao-Yang Hospital from January 2014 to December 2020 were eligible to enter our study [17, 18]. Enrolled patients were prospectively followed from diagnosis to death, loss to follow-up or censoring date (November 2022), with the median follow-up period being 1738 days (1690–1786 days). Eligibility criteria included histological confirmation of NSCLC diagnosis, detection of EGFR mutation/Kirsten rat sarcoma viral oncogene (KRAS) mutation/ALK rearrangement detection and high-resolution computed tomography (HRCT). Patients were excluded if they had insufficient clinical data available. Permission for data analysis was approved by the Ethics Committee of the Beijing Chao-Yang Hospital, Beijing Institute of Respiratory Medicine, Capital Medical University, Beijing, China (No. 2021-ke-443), and written informed consent was obtained from all patients.

Data collection

Demographic data, comorbidity-related factors, tumour-related factors and treatment-related factors were obtained from Electronic Medical Records. A subset of participants also underwent pre-bronchodilator spirometry at diagnosis, and forced expiratory volume in 1 s per forced vital capacity (FEV_1/FVC) $\leqslant$70% was defined as airway obstruction. COPD severity was assessed based on pulmonary function test (PFT). Participants with FEV_1 >80%, 80% but $\geqslant$50% or 50% but $\geqslant$30% or $\leqslant$30% were classified as mild, moderate, severe and very severe, respectively [19]. The patients involved were staged according to the classification of TNM of the International Association for the Study of Lung Cancer (version 8) [20] and divided into localised stages, including stage I, II and III A, and advanced stages, including stage III B, III C and IV. Detailed methods about genotype evaluation techniques have been provided in our previous publications [17, 21].

Assessment of CT-defined emphysema

CT-defined emphysema was defined as disrupted lung vasculature and parenchyma with low attenuation that occupies any lung zone in HRCT [22]. It was diagnosed by two pulmonologists from HRCT scans of the chest for visual assessment, and discordances were adjudicated by a thoracic radiologist. Patients were dichotomised according to the presence or absence of the CT-defined emphysema. For patients with CT-defined emphysema, visual assessment of CT scans to describe subtypes based on the Fleischner Society guidelines was performed [22]. CT-defined emphysema is classified as centrilobular and paraseptal, while panlobular emphysema was not used in this study because it associates with α_1-antitrypsin deficiency [22, 23]. Further, we quantified the severity on the baseline screening CT scan. The Hounsfield unit (HU) threshold for low attenuation area (LAA) in quantitative assessments was defined using −950 HU [24, 25]. Furthermore, subjects with CT-defined emphysema were then divided into those with mild (LAA% $\leqslant$9%) and those with moderate–severe (LAA% >9%) emphysema [25].

Imaging of HRCT

All included patients underwent 64-slice spiral CT (Siemens Healthcare, Forchheim, Germany) at the time of diagnosis. HRCT examinations were acquired from a single breath-held scanning at end-inspiration for the scope from the apex of the lung to the diaphragm. Images were displayed at window settings appropriate for viewing the lung parenchyma (lung window setting: level −450 HU; width 1300 HU; and mediastinal window settings: level 40 HU; width 400 HU). Image quantitative assessments were performed

on AW 4.7 Server workstation (GE Healthcare, Chicago, IL, USA) using advanced application Thoracic VCAR software.

Statistical analysis

Mean±SD or median (interquartile range) were used to describe continuous variables as appropriate. Categorical variables were described as frequencies and percentages. The association between CT-defined emphysema and patient characteristics was evaluated using logistic regression. And Cox regression was performed to analyse the associations between CT-defined emphysema with OS. The differences in survival between groups were derived by Kaplan–Meier analysis and log-rank testing. Statistical significance was defined as a two-tailed p-value of <0.05 for all tests. Statistical analyses were performed with SPSS version 21.0 and R version 4.1.0. A professional epidemiologist reviewed the study.

Results

Participant characteristics

A total of 869 NSCLC patients were initially enrolled in this study. 15 patients were excluded due to absent HRCT at baseline (n=6) and insufficient clinical records (n=9) (figure 1). Thus, 854 eligible patients were included in this study. The median follow-up for OS was 1738 days. Finally, 29 patients were lost to follow-up, predominantly owing to an inability to contact patients by phone for assessment. 393 patients were alive and censored at last follow-up.

The clinicopathological characteristics of the study participants are summarised in table 1. The median age of all patients was 62 years and 61.9% of the patients were older than 60 years. Male patients (55.4%) and people who never smoke (54.8%) were predominant in this study. Regarding the oncogene status, the respective proportions of identified driver oncogene types for EGFR mutated/KRAS mutated/ALK rearranged were 37.8%/10.7%/9.3%.

CT-defined emphysema was present in 300 (35.1%) patients at diagnosis. 162 patients' tumours were located in an emphysematous area, and the histological type in 68.5% (111 out of 162) patients was

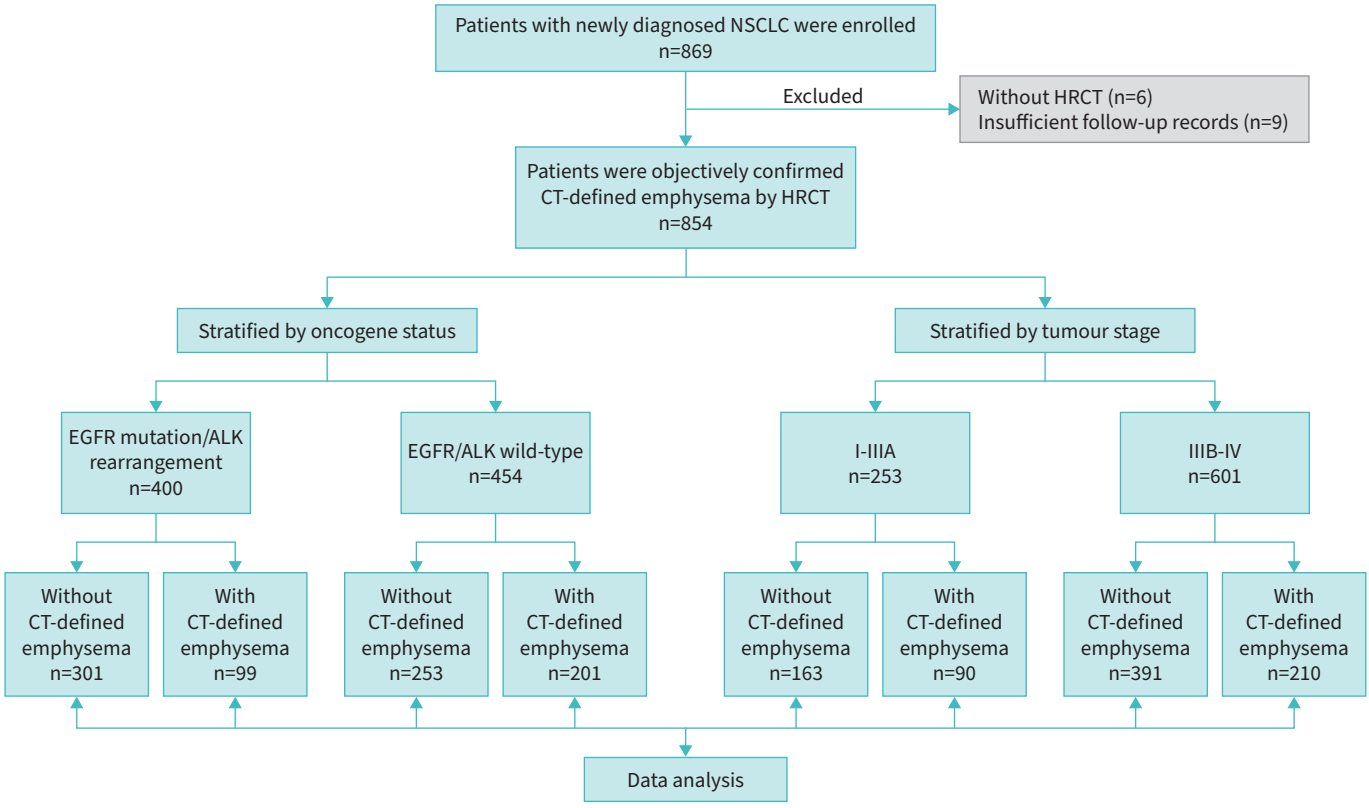

FIGURE 1 Study flow diagram. CT: computed tomography; HRCT: high-resolution computed tomography; NSCLC: nonsmall cell lung cancer; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase.

TABLE 1 Baseline characteristics of patients

Patient characteristics	All patients[#]	Patients with CT-defined emphysema[¶]			Patients without CT-defined emphysema[+]	p-value[§]
		All Patients with CT-defined emphysema	Mild (LAA% ⩽9%)[f]	Moderate/severe (LAA% >9%)[##]		
Age years						
Median (range)	62 (55–69)	65 (59–70)	64 (58–70)	66 (60–71)	61 (54–68)	<0.001
<60	325 (38.1)	82 (25.2)	51 (15.7)	31 (9.5)	243 (74.8)	
⩾60	529 (61.9)	218 (41.2)	102 (19.3)	116 (21.9)	311 (58.8)	
Sex						<0.001
Male	473 (55.4)	245 (48.2)	119 (25.2)	126 (26.6)	228 (48.2)	
Female	381 (44.6)	55 (14.4)	34 (8.9)	21 (5.5)	326 (85.6)	
BMI kg·m^{-2}	24.0±3.4	23.6±3.4	24.0±3.4	23.3±3.5	24.2±3.3	0.013
Smoking status						<0.001
Yes	386 (45.2)	203 (52.6)	96 (24.9)	107 (27.7)	183 (47.4)	
No	468 (54.8)	97 (20.7)	57 (12.2)	40 (8.5)	371 (79.3)	
Comorbidity types						
Hypertension	326 (38.2)	113 (34.7)	55 (16.9)	58 (17.8)	213 (65.3)	0.823
Diabetes mellitus	128 (15.0)	45 (35.2)	22 (17.2)	23 (18.0)	83 (64.8)	0.994
VTE	65 (7.6)	18 (27.7)	9 (13.8)	9 (13.8)	47 (72.3)	0.191
Cerebrovascular disease	57 (6.7)	23 (40.4)	12 (21.1)	11 (19.3)	34 (59.6)	0.393
ECOG PS						0.200
0–2	659 (77.2)	224 (34.0)	117 (17.8)	107 (16.2)	435 (66.0)	
3–4	195 (22.8)	76 (39.0)	36 (18.5)	40 (20.5)	119 (61.0)	
Tumour stage						<0.001
I	115 (13.5)	29 (25.2)	12 (10.4)	17 (14.8)	86 (74.8)	
II	89 (10.4)	38 (42.7)	25 (28.1)	13 (14.6)	51 (57.3)	
IIIA	49 (5.7)	23 (46.9)	12 (24.5)	11 (22.4)	26 (53.1)	
IIIB	60 (7.0)	38 (63.3)	22 (36.7)	16 (26.7)	22 (36.6)	
IV	541 (63.3)	172 (31.8)	82 (15.2)	90 (16.6)	369 (68.2)	
Tumour histology						<0.001
Adenocarcinoma	678 (79.4)	208 (30.7)	110 (16.2)	98 (14.5)	470 (69.3)	
Non-adenocarcinoma	176 (20.6)	92 (52.3)	43 (46.7)	49 (27.8)	84 (47.7)	
Squamous cell carcinoma	163 (19.1)	85 (52.1)	39 (23.9)	46 (28.2)	78 (47.9)	
Other NSCLC	13 (1.5)	7 (53.8)	4 (30.8)	3 (23.1)	6 (46.1)	
***EGFR* gene**						<0.001
Wild	531 (62.2)	217 (40.9)	110 (20.7)	107 (20.2)	314 (59.1)	
Mutated	323 (37.8)	83 (25.7)	43 (13.3)	40 (48.2)	240 (74.3)	
***KRAS* gene**						0.810
Wild	763 (89.3)	267 (35.0)	140 (18.3)	127 (16.6)	496 (65.0)	
Mutated	91 (10.7)	33 (36.3)	13 (14.3)	20 (22.0)	58 (63.7)	
***ALK* gene**						0.004
Wild	775 (90.7)	284 (36.6)	144 (18.6)	140 (18.0)	491 (63.4)	
Rearranged	79 (9.3)	16 (20.3)	9 (11.4)	7 (8.9)	63 (79.7)	
Treatment method						<0.001
TKI	283 (33.1)	75 (26.5)	37 (13.1)	38 (13.4)	208 (73.5)	
Without TKI	571 (66.9)	225 (39.4)	116 (20.3)	109 (19.1)	346 (60.6)	
Chemotherapy	311 (36.4)	134 (43.1)	72 (23.2)	62 (19.9)	177 (56.9)	
Other	260 (30.4)	91 (35.0)	44 (16.9)	47 (18.1)	156 (65.0)	
Surgery						0.630
Yes	230 (26.9)	82 (35.7)	45 (19.6)	37 (16.1)	148 (64.3)	
No	624 (73.1)	218 (35.0)	108 (17.3)	110 (17.6)	406 (65.0)	
Tumour location 1						0.803
Central	310 (36.3)	106 (34.2)	55 (17.7)	51 (16.5)	204 (65.8)	
Peripheral	523 (61.3)	187 (35.8)	96 (18.4)	91 (17.4)	336 (64.2)	
Diffuse	20 (2.3)	6 (30)	2 (10.0)	4 (20.0)	14 (70)	
Tumour location 2						0.917
Right	331 (38.8)	114 (34.4)	65 (19.6)	49 (14.8)	217 (65.6)	
Left	496 (58.1)	177 (35.7)	82 (16.5)	95 (19.2)	319 (64.3)	
Both	27 (3.2)	9 (33.3)	6 (22.2)	3 (11.1)	18 (66.7)	

Continued

TABLE 1 Continued

Patient characteristics	All patients[#]	Patients with CT-defined emphysema[¶]			Patients without CT-defined emphysema[+]	p-value[§]
		All Patients with CT-defined emphysema	Mild (LAA% ⩽9%)[f]	Moderate/severe (LAA% >9%)[##]		
Tumour in emphysematous area						
Yes	-	162	67 (41.4)	95 (58.6)	-	-
No	-	138	86 (62.3)	52 (37.7)	-	-
Emphysema location						
Upper lung predominant	-	110	79 (71.8)	31 (28.2)	-	-
Lower lung predominant	-	10	6 (60.0)	4 (40.0)	-	-
Diffuse	-	171	59 (34.5)	112 (65.5)	-	-
Emphysema subtype						
CLE	-	201	108 (53.7)	93 (46.3)	-	-
PSE	-	99	45 (45.5)	54 (54.5)	-	-

Data are presented as mean±SD and median (interquartile range) for continuous variables, and n (%) for categorical. CT: computed tomography; LAA: low attenuation area; BMI: body mass index; VTE: venous thromboembolism; ECOG PS: Eastern Cooperative Oncology Group Performance Status; NSCLC: nonsmall cell lung cancer; EGFR: epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral oncogene; ALK: anaplastic lymphoma kinase; TKI: tyrosine kinase inhibitors; CLE: centrilobular emphysema; PSE: paraseptal emphysema. [#]: n=854; [¶]: n=300; [+]: n=554; [§]: p-value tests for differences between the patients with CT-defined emphysema and the patients without CT-defined emphysema two groups; [f]: n=153; [##]: n=147.

adenocarcinoma. Moreover, 153 (51.0%) had LAA% ⩽9% and 147 (49.0%) had LAA% >9%. CT-defined emphysema was predominantly located in upper lobe lung in the mild group (LAA% ⩽9%) but was distributed more diffusely in the moderate or severe group (LAA% >9%). Centrilobular emphysema (CLE) was the predominant type in our cohort (67.0%, 201 out of 300). 108 (53.7%) CLE had LAA% ⩽9% and 93 (46.3%) had LAA% >9%, respectively. No significant associations were found between tumour location and tumour histology (p=0.740) or molecular markers (all p>0.05) (supplementary e-table 1).

Association between CT-defined emphysema and patient characteristics

Bivariate analyses revealed that EGFR wild-type (odds ratio (OR) 1.998; 95% confidence interval (CI) 1.475–2.707; p<0.001) and ALK wild-type (OR 2.277; 95% CI 1.291–4.018; p=0.004) were significantly associated with the presence of CT-defined emphysema (table 2). 62.3% of the EGFR/ALK wild-type cases were in patients who were currently smoking or used to smoke. Among EGFR or/and ALK wild-type patients, the presence of CT-defined emphysema correlated with smoking status (all p<0.001) (supplementary e-table 2).

TABLE 2 The association between patient characteristics and CT-defined emphysema

Variables	Bivariate analysis	
	OR (95% CI)	p-value
Age (⩾60 *versus* <60 years)	2.077 (1.532–2.816)	< 0.001
Sex (male *versus* female)	6.369 (4.543–8.929)	< 0.001
BMI (⩾25 *versus* <25 kg·m^{-2})	0.720 (0.534–0.971)	0.031
Smoking history (yes *versus* no)	4.243 (3.144–5.726)	< 0.001
ECOG PS (3–4 *versus* 0–2)	1.240 (0.892–1.725)	0.201
***EGFR* gene (wild *versus* mutated)**	1.998 (1.475–2.707)	< 0.001
***KRAS* gene (wild *versus* mutated)**	0.946 (0.602–1.488)	0.810
***ALK* gene (wild *versus* rearranged)**	2.277 (1.291–4.018)	0.004

CT: computed tomography; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral oncogene; ALK: anaplastic lymphoma kinase.

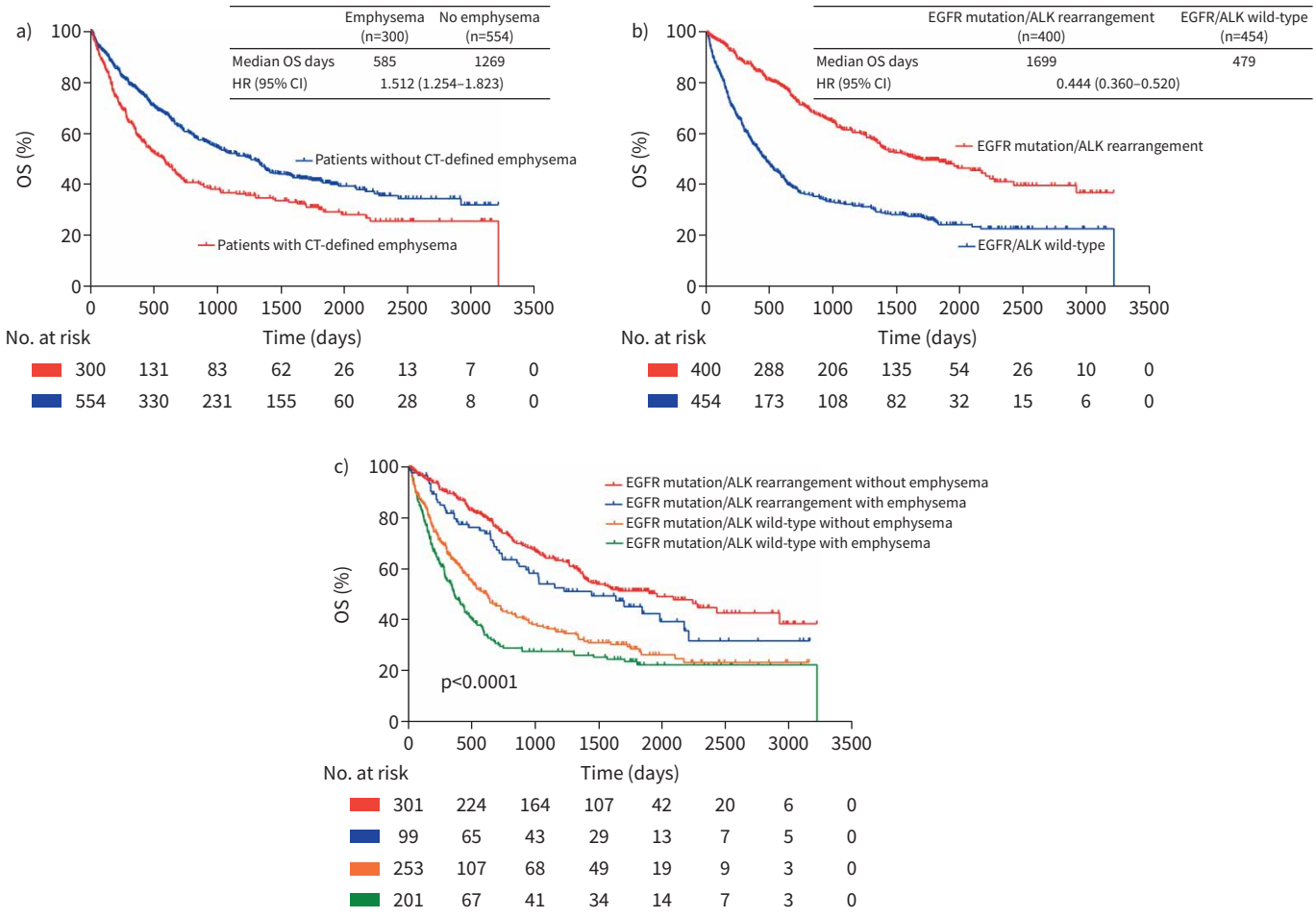

FIGURE 2 a) Kaplan–Meier curves showing patients with CT-defined emphysema had worse OS compared with those without CT-defined emphysema. b) Kaplan–Meier curves showing patients with EGFR/ALK wild-type had worse OS compared with those with EGFR mutation/ALK rearrangement. c) Kaplan–Meier curves showing OS rate among the driver oncogene groups with different CT-defined emphysema status differed significantly (log-rank p<0.001). EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; CT: computed tomography; OS: overall survival.

Association between CT-defined emphysema and OS

The Kaplan–Meier survival analyses showed that patients with CT-defined emphysema had significantly worse survival compared to those without it (median, 585 days *versus* 1269 days; hazard ratio (HR) 1.512; 95% CI 1.254–1.823; p<0.001) (figure 2a). CT-defined emphysema remained a significant predictor of poorer OS when controlled for age, sex, smoking history, tumour histology and Eastern Cooperative Oncology Group Performance Status (ECOG PS), whether in I-IIIA stage (adjusted HR 1.745; 95% CI 1.102–2.763, p=0.017) or in IIIB-IV stage (adjusted HR 1.291; 95% CI 1.037–1.606, p=0.022) (table 3).

TABLE 3 Multivariable Cox regression analyses of CT-defined emphysema status with overall survival

	HR	95% CI	Adjusted p-value
I-IIIA (n=253)			
CT-defined emphysema (yes or no)	1.745	1.102–2.763	0.017
IIIB-IV (n=601)			
CT-defined emphysema (yes or no)	1.291	1.037–1.606	0.022

Note: The multivariate Cox regression analysis is adjusted for age, sex, smoking history, tumour histology and ECOG PS. CT: computed tomography; HR: hazard ratio.

We evaluated the association between CT-defined emphysema and OS stratified by oncogene status (figure 2). Patients with EGFR mutations/ALK rearrangements compared with wild-type cases experienced remarkably improved survival outcomes (median 1699 *versus* 479 days; HR 0.444; 95% CI 0.360–0.520; p<0.001) (figure 2b). Kaplan–Meier curves showed OS rate among the driver oncogene groups with different CT-defined emphysema status differed significantly (log-rank p<0.001). More specifically, the presence of CT-defined emphysema was associated with worse OS among the patients with EGFR/ALK wild-type (median 365 *versus* 623 days; HR 0.779; 95% CI 0.612–0.980; p=0.034) (figure 2c). When the analysis was limited to the patients with EGFR mutations/ALK rearrangement, no relationship between CT-defined emphysema and the OS rate was observed (median 1443 *versus* 1957 days; HR 0.762; 95% CI 0.523–1.065; p=0.107).

Subsequently, analysis showed that 258 patients who experienced death were staged as IIIB-IV, and their risk of mortality was 3.782-fold higher than that of patients as I-IIIA (figure 3a). In the stratified analysis, there were significant differences in the rate of OS among the tumour stage groups with different CT-defined emphysema status based on the log-rank tests (p<0.001) (figure 3b).

Stratified survival analysis by severity of CT-defined emphysema was analysed. Kaplan–Meier curves showed no significant difference between the mild (LAA% ⩽9%) and moderate–severe group (LAA% >9%) (median 590 *versus* 543 days; HR 1.096; 95% CI 0.822–1.465; p=0.532) (supplementary e-figure 1a). In order to screen out the patients with the worst prognosis, a new cut-off value (17%) to distinguish different severity was calculated using receiver operating characteristic curve. CLE with LAA% >17% displayed poorer survival than those with LAA% ⩽17% (median 432 *versus* 670 days; HR 1.564; 95% CI 1.085–2.518; p=0.020) (supplementary e-figure 1b).

Furthermore, Kaplan–Meier curves showed OS rate among treatment received and year of diagnosis groups with different CT-defined emphysema status differed significantly (both log-rank p<0.001) (supplementary e-figure 2). Male patients had worse OS compared with female, and male patients with CT-defined emphysema displayed poorer survival than those without CT-defined emphysema (supplementary e-figure 3).

Association between airway obstruction and OS

Overall, 57.7% (493 out of 854) of the patients had both spirometry and CT data available. 157 out of 493 patients (31.8%) had airway obstruction on spirometry (supplementary e-table 3). We performed a sensitivity analysis only including those with spirometry. The median survival of the airway obstruction group was significantly shorter than that of the non-airway obstruction group (median 898 *versus* 1415 days; HR 1.431; 95% CI 1.114–1.956; p=0.301) (figure 4).

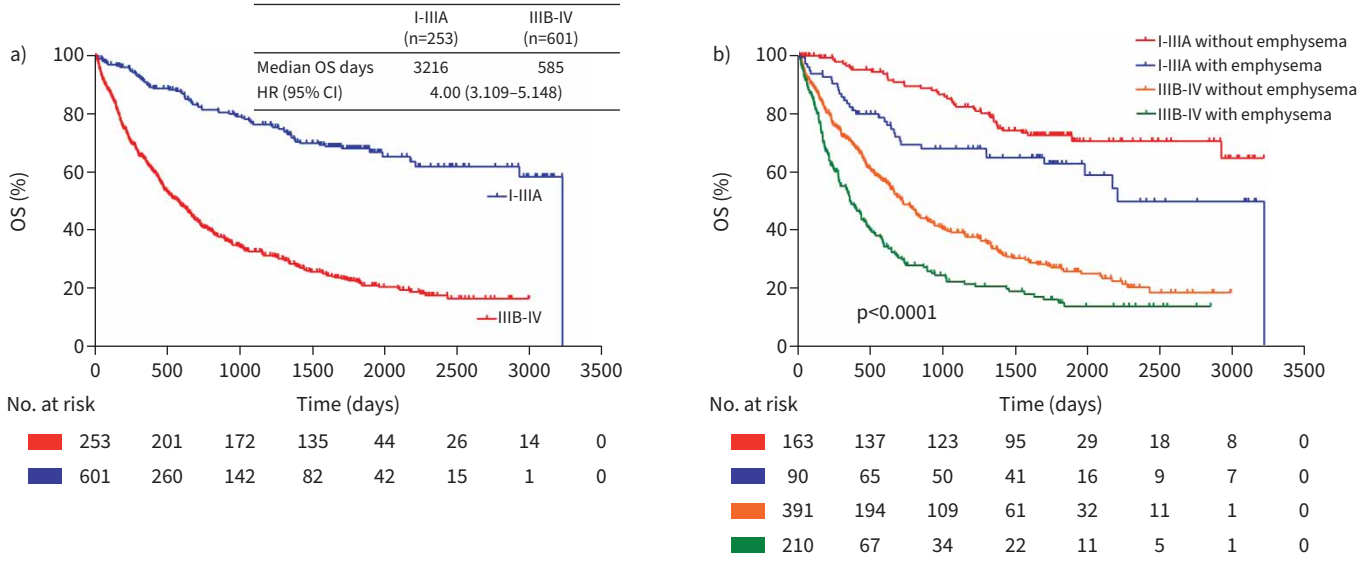

FIGURE 3 a) Kaplan–Meier curves showing patients staged as IIIB-IV had worse OS than I-IIIA patients. b) Kaplan–Meier curves showing OS rate among the tumour stage groups with different CT-defined emphysema status differed significantly (log-rank p<0.001). OS: overall survival.

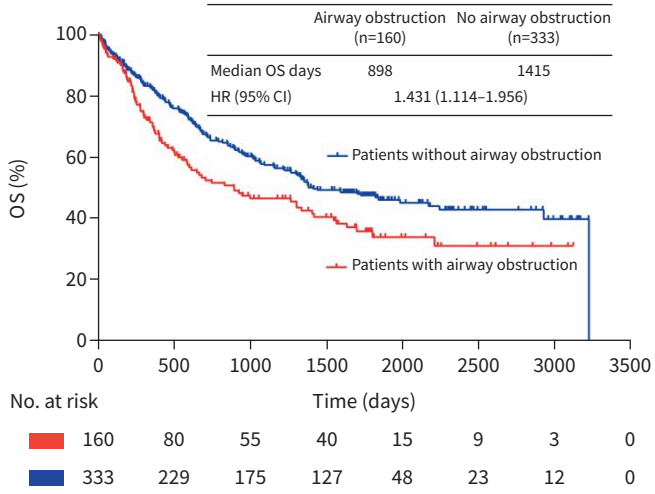

FIGURE 4 Kaplan–Meier curves showing patients with airway obstruction had worse overall survival (OS) compared with those without airway obstruction.

CT-defined emphysema and spirometry

Among individuals who had both spirometry and CT data available, 38.9% (192 out of 493) had CT-defined emphysema. Roughly 80% of patients are graded as mild and moderate in our study (supplementary e-table 3). 54.7% had CT-defined emphysema but normal spirometry. Additionally, PFT severity score correlates with emphysema severity (Kendall's tau-b=0.311, p=0.003) and emphysema site (Kendall's tau-b=0.207, p=0.048) significantly.

Discussion

To our knowledge, this is the first prospective cohort study to characterise CT-defined emphysema and investigate its potential impact on NSCLC prognosis in the molecular era. We demonstrate that CT-defined emphysema is more common in EGFR and ALK wild-type. We also suggest that NSCLC patients with CT-defined emphysema have a worse OS. Importantly, CLE with LAA% >17% was associated with poorer survival in patients with CT-defined emphysema.

It was reported that the prevalence of emphysema detected on CT in NSCLC patients ranged from 31.2% to 58.0% [10, 26], which was relatively higher than our result (35.1%). Perhaps this study enrolled patients in this cohort who underwent genetic testing and had a relatively high proportion of adenocarcinoma (79.4%), decreasing the prevalence of CT-defined emphysema. There is wide geographic and ethnic variation in the prevalence of CT-defined emphysema. Previous studies have shown that Americans and the British have a much higher incidence [8, 27, 28]. The Genetic Epidemiology of COPD Study confirmed that there are racial differences in the severity of emphysema [29] and pathogenesis for the differences may encompass genetic or epigenetic effects, immune system response and demographic characteristics [30].

Notably, EGFR and ALK wild-type are significantly associated with the presence of CT-defined emphysema in the bivariate analysis, implying a potential association between oncogene status and CT-defined emphysema. Similarly to our findings, prior studies found that the frequency of EGFR mutation was lower in patients with CT-defined emphysema [13–16]. Patients with EGFR mutations who did not smoke were less likely to have CT-defined emphysema, and a plausible reason is that most NSCLC patients with EGFR mutation have a history of non-smoking [13]. Regarding the status of ALK, Rizzo *et al*. [16] did not find any correlation between ALK wild-type and CT-defined emphysema even in the univariate analysis. However, the correlation and mechanism between underlying lung diseases and oncogene status in NSCLC have not been thoroughly investigated.

In the present study, it appears that CT-defined emphysema has prognostic significance in patients with NSCLC even after accounting for covariables. Our results further support that the presence of CT-defined emphysema, even if patients are asymptomatic and without airway obstruction, represents genuine lung disease [24, 28, 31]. Young *et al*. [32]found that the risk of dying of lung cancer increased with worsening

airway obstruction. However, it is not cost-effective to perform spirometry for all patients because currently there is a paucity of evidence to prove that screening spirometry has net benefit [33, 34]. Lin *et al*. [35] reviewed randomised controlled trials of any screening method including spirometry, questionnaire or risk assessment followed by spirometry, and concluded that screening for COPD does not improve health-related quality of life or reduce morbidity or mortality. Adams *et al*. [36] showed that combined screening for lung cancer and COPD using low-dose CT might help to re-evaluate screening benefit in subjects with emphysema and determine the risk of competing causes of death. We contend that it is prudent to identify CT-defined emphysema in pretreatment CT images, rather than focusing on airway obstruction by spirometry, as CT data are more commonly available for lung cancer patients. Overall, an accurate and cost-effective screening approach should be assessed in future.

In the past decades, a few studies have reported correlations between CT-defined emphysema and survival (table 4). The different outcomes recorded in the literature between CT-defined emphysema and survival may be related to the target population, study sample size and different ethnicities. Two retrospective cohort studies in African American patients and Japanese patients have found that CT-defined emphysema was not associated with a worse prognosis [7, 8]. The discrepancy in the results between these studies and ours may be explained by several reasons. Firstly, these studies follow a retrospective cohort design in which relatively small sample sizes are used in the analyses. The Japanese study only enrolled NSCLC patients who underwent complete resection [7], while in our study, the prospective cohort included newly diagnosed NSCLC. Secondly, the proportion of patients with CT-defined emphysema that were included in the studies was 75% in African American patients and 27% in Japanese patients, respectively. Lastly, the method to determine the presence of CT-defined emphysema was evaluated by a semiquantitative method in African American patients and by visual assessment in Japanese patients and ours.

To date, relatively few studies have investigated the relationships between CT-defined emphysema, oncogene status and prognosis among NSCLC patients. The stratified analysis demonstrated that the group with EGFR mutations/ALK rearrangements who did not have CT-defined emphysema displayed the highest OS rate, whereas the EGFR/ALK wild-type group who had CT-defined emphysema showed the poorest survival. In patients who are driver oncogene positive, tyrosine kinase inhibitor therapy could abrogate the risks of CT-defined emphysema on patient survival [37]. In the EGFR/ALK wild-type subgroup, CT-defined emphysema may contribute predominantly to the prognosis. In view of the fact that TNM classification is the leading predictor of prognosis in NSCLC [20], we further stratify patients by tumour stage and find that CT-defined emphysema is a significant established risk factor regardless of tumour stage. This is congruent with the results in previous studies among patients with surgically resected, localised stage lung cancer [10, 38].

To screen out the patients with the worst prognosis, we adapted a new cut-off value (17%) to distinguish between different severities and found that CLE with LAA% >17% displayed poorer survival. This result was similar to those of Shiraishi *et al*. [39], which suggested that the moderate or more severe CLE was associated with higher long-term mortality among patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 or higher. Therefore, we believed that identifying patients with CLE with LAA% >17% could help clinicians prioritise more intensive surveillance and individualised treatment,

TABLE 4 Characteristics of studies that assessed CT-defined emphysema

Study	Country	Study type	Population	Assessment method	Imaging examination	Prevalence %	Predictor of survival
Ueda K *et al*. [10]	Japan	Prospective	100 NSCLC	Quantitative	HRCT	58	Yes
Gullón JA *et al*. [26]	Spain	Prospective	359 NSCLC	Quantitative	HRCT	31	Yes
Zulueta JJ *et al*. [31]	USA	Prospective	9047 smokers	Visual	LDCT	29	Yes
Mina N *et al*. [8]	USA	Retrospective	114 NSCLC	Visual	HRCT	75	No
Bishawi M *et al*. [27]	USA	Retrospective	153 NSCLC	Visual	HRCT	75	Yes
Kumagai S *et al*. [7]	Japan	Retrospective	365 NSCLC	Visual	HRCT	27	No
Lynch DA *et al*. [28]	USA	Retrospective	3171 smokers	Visual	HRCT	66	Yes
Labaki WW *et al*. [24]	USA	RCT	7262 smokers	Quantitative	LDCT	45	Yes
Yasuura Y *et al*. [9]	Japan	Retrospective	1062 NSCLC	Quantitative	LDCT	14	Yes
Current study	China	Prospective	854 NSCLC	Visual	HRCT	35	Yes

CT: computed tomography; NSCLC: nonsmall cell lung cancer; HRCT: high-resolution computed tomography; LDCT: low-dose computed tomography.

including optimisation of medication therapy and nonpharmacological approaches, such as pulmonary rehabilitation and education. However, the mechanistic links on how CT-defined emphysema affects survival in NSCLC have not been elaborated [38, 40].

Our study has several limitations. Firstly, considering the high ratio of alive patients at the end of follow-up in our cohort, there was a relatively high proportion of censored data, which may affect the power of this study. But significant differences were detectable in our results. Secondly, not all individuals were tested for spirometry, so the analysis for airway obstruction was limited to small size subgroups of patients. Finally, even though this prospective cohort study enrolled a relatively large sample size, it was a single-centre study and may have potential biases limiting the generalisability of our results.

In conclusion, CT-defined emphysema is an independent predictor for NSCLC prognosis, and CLE (LAA % >17%) displayed poorer survival. Clinicians should pay more attention to the detrimental impact of CT-defined emphysema on NSCLC patients to ensure early interventions and provide precision management. Moreover, prospective studies are needed to further explore this association.

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Data availability statement: Data are available upon reasonable request, to be made to the corresponding author.

Author contributions: Y. Zhang is the guarantor of this article. Y. Zhang, J. Yi, K. Huang, X. Guo and Y. Zhang participated and conceived the study design. Y. Zhang, J. Yi, D. Sun, Y. Su, Z. Ma, M. Zhu and S. Zhang contributed to the data collection, patients recruited, treated and followed-up. X. Guo contributed to visual and quantitative assessments of CT-defined emphysema. Y. Zhang, J. Yi, D. Sun and Y. Zuo analysed the data. Y. Zhang and J. Yi wrote the first manuscript draft. All the authors reviewed the final version of the manuscript.

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References

1 Siegel RL, Miller KD, Fuchs HE, *et al.* Cancer statistics, 2022. *CA Cancer J Clin* 2022; 72: 7–33.
2 Travis WD, Brambilla E, Noguchi M, *et al.* International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011; 6: 244–285.
3 Yong PC, Sigel K, de-Torres JP, *et al.* The effect of radiographic emphysema in assessing lung cancer risk. *Thorax* 2019; 74: 858–864.
4 Yang X, Wisselink HJ, Vliegenthart R, *et al.* Association between chest CT-defined emphysema and lung cancer: a systematic review and meta-analysis. *Radiology* 2022; 304: 322–330.
5 Mouronte-Roibás C, Leiro-Fernández V, Ruano-Raviña A, *et al.* Chronic obstructive pulmonary disease in lung cancer patients: prevalence, underdiagnosis, and clinical characterization. *Respiration* 2018; 95: 414–421.
6 Gao YH, Guan WJ, Liu Q, *et al.* Impact of COPD and emphysema on survival of patients with lung cancer: a meta-analysis of observational studies. *Respirology* 2016; 21: 269–279.
7 Kumagai S, Marumo S, Yamanashi K, *et al.* Prognostic significance of combined pulmonary fibrosis and emphysema in patients with resected non-small-cell lung cancer: a retrospective cohort study. *Eur J Cardiothorac Surg* 2014; 46: e113–e119.
8 Mina N, Soubani AO, Cote ML, *et al.* The relationship between chronic obstructive pulmonary disease and lung cancer in African American patients. *Clin Lung Cancer* 2012; 13: 149–156.

9 Yasuura Y, Terada Y, Mizuno K, *et al.* Quantitative severity of emphysema is related to the prognostic outcome of early-stage lung cancer. *Eur J Cardiothorac Surg* 2022; 62: ezac499.
10 Ueda K, Jinbo M, Li TS, *et al.* Computed tomography-diagnosed emphysema, not airway obstruction, is associated with the prognostic outcome of early-stage lung cancer. *Clin Cancer Res* 2006; 12: 6730–6736.
11 Daly ME, Singh N, Ismaila N, *et al.* Management of Stage III Non-Small-Cell Lung Cancer: ASCO Guideline. *J Clin Oncol* 2022; 40: 1356–1384.
12 Ettinger DS, Wood DE, Aisner DL, *et al.* Non-small cell lung cancer, Version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2022; 20: 497–530.
13 Liu Q, Huang Q, Yu Z, *et al.* Clinical characteristics of non-small cell lung cancer patients with EGFR mutations and ALK&ROS1 fusions. *Clin Respir J* 2022; 16: 216–225.
14 Yang X, Liu M, Ren Y, *et al.* Using contrast-enhanced CT and non-contrast-enhanced CT to predict EGFR mutation status in NSCLC patients: a radiomics nomogram analysis. *Eur Radiol* 2022; 32: 2693–2703.
15 Liu Y, Kim J, Qu F, *et al.* CT Features associated with epidermal growth factor receptor mutation status in patients with lung adenocarcinoma. *Radiology* 2016; 280: 271–280.
16 Rizzo S, Petrella F, Buscarino V, *et al.* CT Radiogenomic characterization of EGFR, K-RAS, and ALK mutations in non-small cell lung cancer. *Eur Radiol* 2016; 26: 32–42.
17 Dou F, Zhang Y, Yi J, *et al.* Association of ALK rearrangement and risk of venous thromboembolism in patients with non-small cell lung cancer: a prospective cohort study. *Thromb Res* 2020; 186: 36–41.
18 Li J, Yi J, Hua L, *et al.* Development and validation of a predictive score for venous thromboembolism in newly diagnosed non-small cell lung cancer. *Thromb Res* 2021; 208: 45–51.
19 Singh D, Agusti A, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. *Eur Respir J* 2019; 53: 1900164.
20 Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM Classification for Lung Cancer. *J Thorac Oncol* 2016; 11: 39–51.
21 Dou F, Li H, Zhu M, *et al.* Association between oncogenic status and risk of venous thromboembolism in patients with non-small cell lung cancer. *Respir Res* 2018; 19: 88.
22 Lynch DA, Austin JH, Hogg JC, *et al.* CT-definable subtypes of chronic obstructive pulmonary disease: a statement of the Fleischner society. *Radiology* 2015; 277: 192–205.
23 Shiraishi Y, Shimada T, Tanabe N, *et al.* The prevalence and physiological impacts of centrilobular and paraseptal emphysema on computed tomography in smokers with preserved ratio impaired spirometry. *ERJ Open Res* 2022; 8: 00063-2022.
24 Labaki WW, Xia M, Murray S, *et al.* Quantitative emphysema on low-dose CT imaging of the chest and risk of lung cancer and airflow obstruction: an analysis of the national lung screening trial. *Chest* 2021; 159: 1812–1820.
25 Mascalchi M, Romei C, Marzi C, *et al.* Pulmonary emphysema and coronary artery calcifications at baseline LDCT and long-term mortality in smokers and former smokers of the ITALUNG screening trial. *Eur Radiol* 2023; 33: 3115–3123.
26 Gullón JA, Suárez I, Medina A, *et al.* Role of emphysema and airway obstruction in prognosis of lung cancer. *Lung Cancer* 2011; 71: 182–185.
27 Bishawi M, Moore W, Bilfinger T. Severity of emphysema predicts location of lung cancer and 5-y survival of patients with stage I non-small cell lung cancer. *J Surg Res* 2013; 184: 1–5.
28 Lynch DA, Moore CM, Wilson C, *et al.* CT-based visual classification of emphysema: association with mortality in the COPDGene study. *Radiology* 2018; 288: 859–866.
29 Hansel NN, Washko GR, Foreman MG, *et al.* Racial differences in CT phenotypes in COPD. *COPD* 2013; 10: 20–27.
30 Siegfried JM. Sex and gender differences in lung cancer and chronic obstructive lung disease. *Endocrinology* 2022; 163: bqab254.
31 Zulueta JJ, Wisnivesky JP, Henschke CI, *et al.* Emphysema scores predict death from COPD and lung cancer. *Chest* 2012; 141: 1216–1223.
32 Young RP, Ward RC, Scott RJ, *et al.* Airflow limitation and mortality during cancer screening in the National Lung Screening Trial: why quantifying airflow limitation matters. *Thorax* 2023; 78: 690–697.
33 Mangione CM, Barry MJ, Nicholson WK, *et al.* Screening for chronic obstructive pulmonary disease: US preventive services task force reaffirmation recommendation statement. *JAMA* 2022; 327: 1806–1811.
34 Lei J, Huang K, Pan J, *et al.* The national COPD screening programme in China: rationale and design. *ERJ Open Res* 2023; 9: 00597-2022.
35 Lin JS, Webber EM, Thomas RG. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Screening for Chronic Obstructive Pulmonary Disease: A Targeted Evidence Update for the US Preventive Services Task Force. Rockville, MD, Agency for Healthcare Research and Quality (US), 2022.
36 Adams SJ, Stone E, Baldwin DR, *et al.* Lung cancer screening. *Lancet* 2023; 401: 390–408.

37 Owen DH, Singh N, Ismaila N, *et al.* Therapy for Stage IV Non-Small-Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2022.2. *J Clin Oncol* 2023: 41: e10-e20.
38 Murakami J, Ueda K, Sano F, *et al.* Pulmonary emphysema and tumor microenvironment in primary lung cancer. *J Surg Res* 2016; 200: 690–697.
39 Shiraishi Y, Tanabe N, Shimizu K, *et al.* Stronger associations of centrilobular than paraseptal emphysema with longitudinal changes in diffusing capacity and mortality in COPD. *Chest* 2023; 164: 327–338.
40 Houghton AM. Mechanistic links between COPD and lung cancer. *Nat Rev Cancer* 2013; 13: 233–245.