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The association and impact of radiographic, pathological emphysema and spirometric airway obstruction on patients with resectable lung adenocarcinoma

Yixiao Zhang[1†], Lu Lang[1†], Xiaojuan Guo[2], Kewu Huang[1], Jiawen Yi[1], Yuan Yuan[1], Min Zhu[1], Shu Zhang[1], Bin Hu[3*], Xue Li[4*] and Yuhui Zhang[1*]

Abstract

Background Destruction of alveoli structure and lung function are interrelated, however, their correlation and clinical significance have been not well defined in patients with lung cancer. Thus, this study aimed to examine the association among radiographic, pathological emphysema and spirometric airway obstruction in patients with resectable lung cancer as well as explore their impact on postoperative pulmonary complications (PPCs) and long-term prognosis.

Methods Lung adenocarcinoma (LUAD) patients who performed chest CT, spirometry, and curative resection were included from a prospective three-institution database. CT-defined emphysema at baseline was assessed visually and quantitatively, pathological emphysema was reviewed on postoperative specimen. Multivariable regression models, propensity score matching, stratified analysis, and subgroup analysis were adopted to reduce selection bias.

Results Our cohort included 902 patients, with a median follow-up of 5.6 years. CT-defined emphysema was present in 163 patients (18.1%) and most of them (86.5%) were validated with pathological evidence. 169 had spirometric airway obstruction, while only 29.6% patients overlapped with CT-defined emphysema. Multivariable logistic regression models showed CT-defined emphysema, not airway obstruction, was associated with an increased risk of PPCs (adjusted odds ratio, 2.35; 95% CI, 1.40–3.93; $P=0.001$). After adjusting for age, sex, body mass index, smoking history, tumour stage, vascular invasion, pleural invasion, multivariate cox analysis identified CT-defined emphysema, not airway obstruction, as an independent prognostic factor for OS (adjusted hazard ratio, 1.44; 95%CI, 1.05–1.97; $P=0.022$). Patients with both radiographic and pathological emphysema experienced worse OS (log-rank $P<0.001$).

†Yixiao Zhang and Lu Lang contributed equally to this work.

*Correspondence:
Bin Hu
hubin705@aliyun.com
Xue Li
pecan08@sina.com
Yuhui Zhang
zhangyhcy@163.com

Full list of author information is available at the end of the article

In the propensity score-matched cohort, stratified analysis, and never-smokers subgroup analysis, CT-defined emphysema remained a strong and statistically significant factor related to poor survival.

Conclusions The presence of radiological and pathological emphysema in resectable LUAD was associated with frequent PPCs and decreased survival.

Clinical trial number Not applicable.

Keywords Emphysema, CT, Lung adenocarcinomas, Complications, Prognosis

Introduction

Lung cancer is the predominant cause of cancer-related deaths globally, accounting for the highest mortality rates in both men and women [1]. Lung adenocarcinoma (LUAD) increasingly becomes the most prevalent subtype over time [2]. Over the past two decades, advances in identifying targetable oncogenic drivers have transformed the management of LUAD, resulting in marked prognostic heterogeneity [3]. Previous studies, including ours, have shown that computed tomography(CT)-defined emphysema increased all-cause mortality in both smoker-based lung cancer screening studies [4–6] and non-small cell lung cancer (NSCLC) cohorts [7–13]. However, whether CT-defined emphysema, spirometric airway obstruction and pathological emphysema demonstrates similar effect in LUAD has been not well defined.

CT-defined emphysema is characterised by low attenuation visible in any lung zone on high-resolution CT scans [14]. Airway obstruction is usually identified on spirometry and caused by a mixture of small airway disease and emphysema [15]. Some researchers have tried to explore the role of CT-defined emphysema and airway obstruction in patients with lung cancer. Ishida et al. founded CT-defined emphysema was associated with postoperative complicationsan and poor prognosis in patients with clinical stage IA NSCLC, but without considering airway obstruction [13]. Another study assessed the impact of both CT-defined emphysema and airflow obstruction on prognosis but did not evaluate their effects on surgical complications in early-stage lung cancer [7]. Moreover, as the diagnosis of CT-defined emphysema is solely based on radiologic evaluation previously, the importance of pathological emphysema in lung cancer has been not fully investigated. Therefore, the associations between CT-defined emphysema, airway obstruction, and pathological emphysema and outcomes, including postoperative pulmonary complications (PPCs) and prognosis, need to be elucidated in patients with resectable LUAD.

Additionally, up to 15% of lung cancer cases in men and 53% in women occur in never-smokers [16]. Lung cancer in smokers and never-smokers exhibits distinct tumour microenvironment and genomic architecture [17]. Yun et al. showed that smokers with CT-defined emphysema had over three times the frequency of prolonged air leak in patients with normal spirometry who underwent lung cancer lobectomy [18]. The impact of CT-defined emphysema in never-smokers and those without spirometric impairment warrants specific attention [19].

In this cohort study, CT-defined emphysema at baseline was assessed visually and quantitatively, and was validated with histopathologically matched abnormalities on surgical specimen. Airway obstruction was diagnosed with spirometry parameters. We aimed to evaluate the impact of CT-defined emphysema, airway obstruction, and pathological emphysema on surgical complications and long-term prognosis during a 10-year follow-up period in operable LUAD patients.

Methods

Study population

A prospectively maintained three-institution departmental database was queried for patients with newly diagnosed primary LUAD who underwent curative resection between January 2014 and December 2020 at Beijing Chao-Yang Hospital [20, 21]. Participants were followed up until February 2024 for vital status determination. Exclusion criteria included adenocarcinoma in situ, neoadjuvant chemotherapy, insufficient tumour characteristics and lack of chest CT scans. Permission for data analysis was granted by the Ethics Committee of the Beijing Chao-Yang Hospital, Beijing Institute of Respiratory Medicine, Capital Medical University, Beijing, China (No. 2024-ke-412 and No. 2021-ke-443) and written informed consent was waived from all patients because of retrospective study design.

Data collection

At baseline, demographic and clinicopathological characteristics (comorbidities, pulmonary function data, cancer details, and surgery-related factors) were obtained from electronic medical records. Pre-bronchodilator forced expiratory volume in one second per forced vital capacity (FEV1/FVC) ≤ 70% was used to define airflow obstruction, while FEV1/FVC > 70.0% indicated normal spirometry [15, 22]. PPCs with grade ≥ 2 within 60 days post-lung cancer surgery, according to the Clavien-Dindo classification system, were considered significant [23]. Specifically, a patient was defined as having a prolonged air leakage if there was a column of air that consistently

crossed into the air leak chamber lasting for more than 5 days. While pneumothorax was defined as requiring chest tube reinsertion within 60 days post-lung cancer surgery. The endpoint was the prognosis of patients, including OS and disease-free survival (DFS). OS was defined as the time interval from the day of surgery to death from any cause. DFS was measured from the surgery date to the date of local or distant recurrence or death from any cause.

Visual and quantitative assessment of CT-defined emphysema

All included patients underwent 64-slice spiral CT (Siemens Healthcare, Forchheim, Germany) within 3 months before surgery. CT-defined emphysema was diagnosed independently by two experienced pulmonologists through visual observation from chest CT scans, with disagreements adjudicated by a mid-career thoracic radiologist. For patients with CT-defined emphysema, visually defined phenotypes were recorded according to the Fleischner Society guidelines [centrilobular emphysema (CLE), paraseptal emphysema (PSE), panlobular emphysema (PLE), and CLE + PSE] [24]. Quantification of emphysema was estimated using commercially available artificial intelligence (AI) software (Thoracic VCAR software) to calculate the percentage of low attenuation areas (%LAAs) at or below − 950 HU relative to the whole-lung volume. The cut-off values (mild ≤ 9%, moderate to severe > 9%) were selected based on ITALUNG trial publications [6]. Detailed methods regarding CT imaging acquisition and evaluation have been described previously [12].

Histopathological evaluation of specimen

LUAD histologic type was evaluated independently by two pathologists with at least 10 years' experience based on the 2021 WHO classification guidelines [2]. Comprehensive methodologies about genotype evaluation techniques have been elucidated in our previous publications [21]. The pathological stage of involved patients was determined or reassessed using the eighth edition of the tumour, nodes and metastasis (TNM) staging system [25]. Emphysema, based on pathological criteria, was defined as permanent abnormal enlarged airspaces distal to the terminal bronchioles, with alveolar wall destruction [14].

Statistical analysis

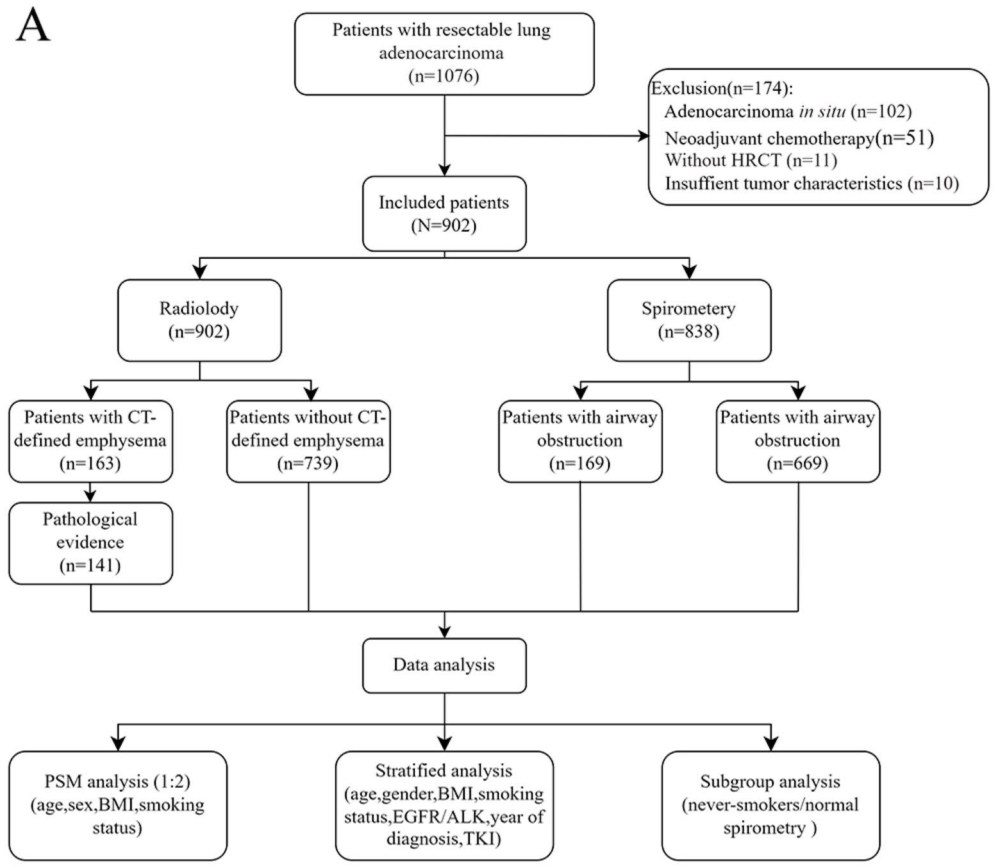
Demographic and clinical data were reported using numbers and percentages for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. Associations between patients with and without CT-defined emphysema were evaluated using the Chi-square test or Fisher exact test for categorical data and the Mann-Whitney U test for continuous variables. Logistic regression was used to investigate the association between CT-defined emphysema and PPCs. Survival rates were calculated using Kaplan-Meier analysis, and differences were analysed using the log-rank test. All factors with a *P*-value of less than 0.2 in univariate analysis were entered into the multivariate analysis with stepwise method. Multivariate Cox proportional hazard models were applied to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of CT-defined emphysema and other potential factors affecting survival. The median follow-up time was calculated using the reverse Kaplan-Meier method. Furthermore, to estimate the strength of associations and reduce selection bias, propensity score matching (PSM), stratified analysis, and subgroup analysis were performed. Propensity scores were calculated using a multiple logistic regression model that included age, sex, body mass index (BMI), and smoking status as variables. Matching was performed at a 1:2 ratio, with a caliper value set at 0.05. The standardized mean difference (SMD) was utilized to assess the degree of PSM. All statistical analyses were conducted using SPSS software version 26.0 (IBM SPSS Statistics for Windows, Version 26.0, IBM Corporation, Armonk, NY, USA) and R software version 4.1.0 (R Version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria). The *P* values were adjusted for multiple comparison correction by using the Benjamini-Hochberg false discovery rate (FDR) method. Statistical significance was defined as $P < 0.05$ for all tests. The study was reviewed by a professional epidemiologist.

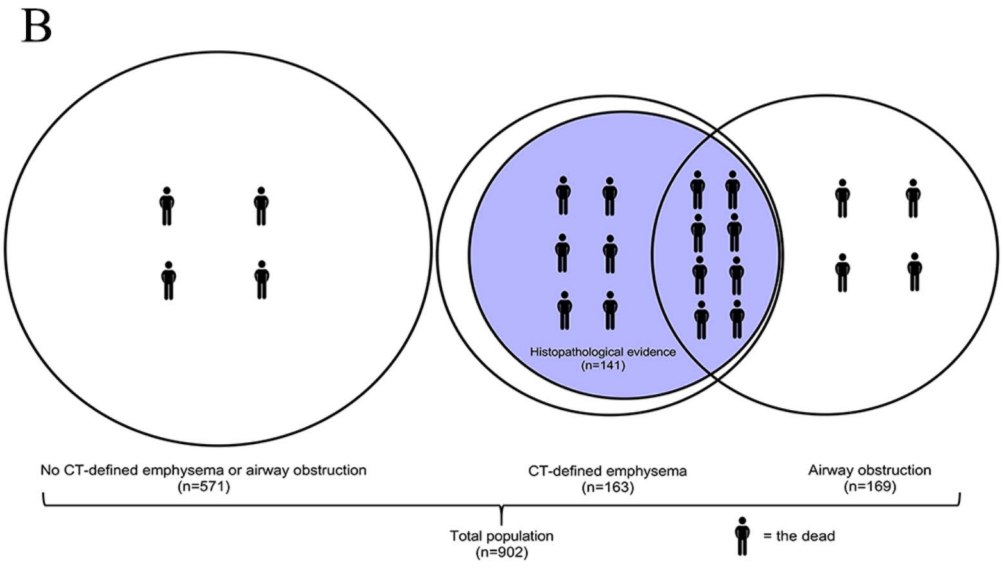
Results

Baseline characteristics

Of the 1,076 patients with LUAD initially enrolled in this study, 174 were excluded due to adenocarcinoma in situ ($n = 102$), neoadjuvant chemotherapy ($n = 51$), absence of baseline CT scans ($n = 11$), and insufficient tumour characteristics ($n = 10$) (Fig. 1a). Therefore, 902 eligible patients were included, with a median follow-up time of 5.6 years (IQR: 4.0-7.5 years). During this period, 393 patients were alive and censored at the last follow-up. Among these, 163 patients (18.1%) had CT-defined emphysema, with 141 out of the 163 confirmed by histopathological evidence. Additionally, 169 patients (20.2%) had airway obstruction on spirometry and only 50 patients overlapped with CT-defined emphysema (Fig. 1b). Figure 2 displays the representative CT imaging, AI analysis, and histopathologically matched abnormalities.

Table 1 and e-Table 1 summarise the baseline characteristics of the 902 participants according to the presence of CT-defined emphysema. Median age was 61 years (IQR: 54–67 years) and 43.3% were male. Compared to patients without CT-defined emphysema, those in the





Group	Number of patients	Median OS,years	Mortality
No CT-defined emphysema and airway obstruction	571	NR	20.0%
All CT-defined emphysema	163	8.77	33.1%
CT-defined emphysema with histopathological evidence	141	8.63	34.8%
CT-defined emphysema with histopathological evidence and airway obstruction	41	7.75	41.5%
Airway obstruction without CT-defined emphysema	119	NR	21.0%

Fig. 1 **A**) Study flow diagram. **B**) Distribution of deaths in LUAD patients according to the presence or absence of CT-defined emphysema, histopathological evidence, and/or airway obstruction. Abbreviations: CT = computed tomography; HRCT = high-resolution computed tomography

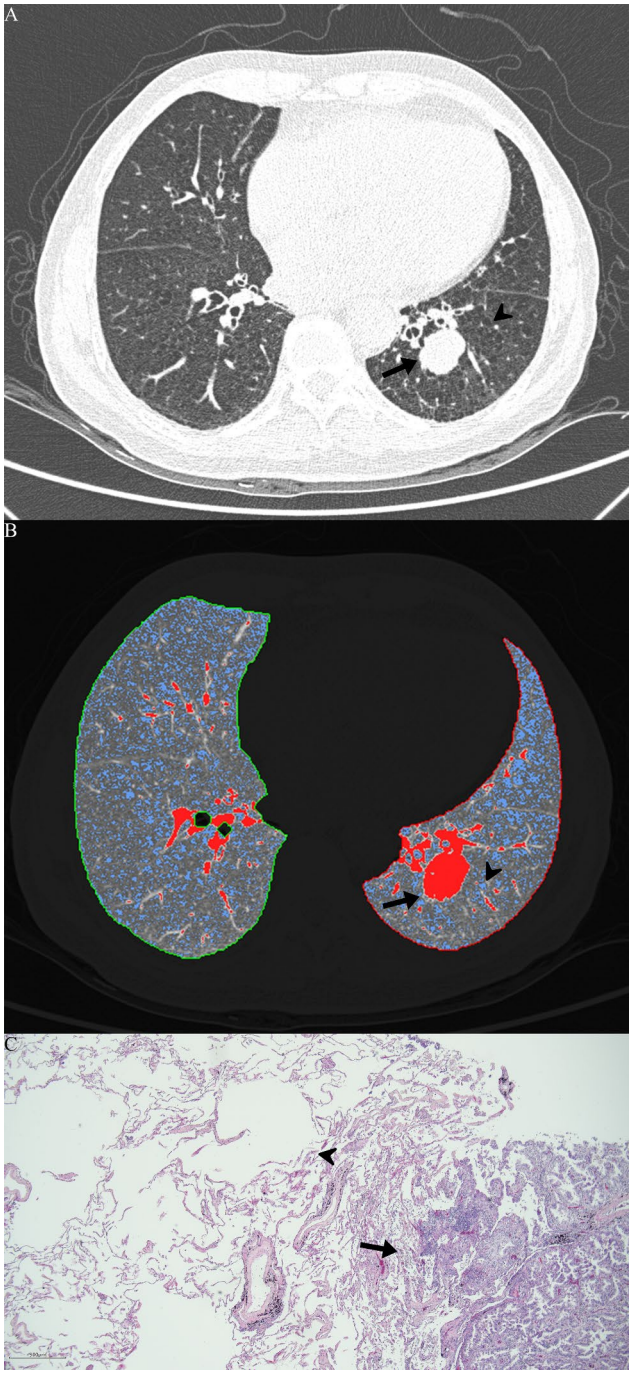


Fig. 2 Representative CT scan, artificial intelligence analysis, and matched pathology of CT-defined emphysema in a 63-year-old male patient with a diagnosis of LUAD who underwent left lower lobectomy. **A**) Lung window images of a CT scan showing centrilobular emphysema in the bilateral lower lobes (arrowhead) with a soild mass (arrow). **B**) Artificial intelligence analysis identifying blue areas as emphysematous lesions(< − 950 Hounsfield units) (arrowhead). **C**) Low-power magnification of LUAD, showing a solid predominant pattern (arrow) in the background of emphysema (arrowhead). Abbreviations: CT = computed tomography; LUAD = lung adenocarcinoma

CT-defined emphysema group were predominantly male (79.8% vs. 35.3%, $P < 0.001$) and had a higher percentage of current/former smokers (55.8% vs. 24.9%, $P < 0.001$). They were also more in pathological stages II/IIIA (I/II/IIIA, 57.7%/23.3%/19.0% vs. 68.1%/18.0%/13.9%, $P = 0.039$) and had larger tumour volumes (T1/T2/T3/T4, 60.7%/29.4%/6.7%/3.1% vs. 74.7%/19.9%/3.1%/2.3%, $P = 0.003$). High-grade histologic patterns, including solid (22.1% vs. 7.4%, $P < 0.001$), micropapillary (8.6% vs. 5.0%, $P = 0.073$), and epidermal growth factor receptor (EGFR) wild-type (46.0% vs. 35.0%, $P = 0.017$) were more prevalent in the emphysematous group. Vascular and pleural invasions were observed in 30.7% and 36.2% of the specimens in the CT-defined emphysema group, significantly more than in the non-CT-defined emphysema group specimens (20.4% and 23.8%, both $P < 0.05$). Additionally, the CT-defined emphysema group showed a greater estimated blood loss and increased length of in-hospital stay (both $P < 0.05$).

Furthermore, among patients with CT-defined emphysema, 65 (39.9%) were categorised as the mild group (LAA% ≤ 9%) and 98 (60.1%) as the moderate or severe group (LAA% > 9%). E-Table 2 details their characteristics. CT-defined emphysema distributed more diffusely in the moderate or severe group than in the mild group (52.0% vs. 36.9%, $P = 0.063$). CLE was the predominant type (108/163, 66.3%), followed by PSE (40/163, 24.5%).

CT-defined emphysema and PPCs

A total of 104 PPCs developed in 90 patients (10.0%) following pulmonary resection (Table 1). The three most common types of PPCs were moderate pleural effusion ($n = 41$), prolonged air leak ($n = 16$), and pneumonia ($n = 15$). A significant increase in the prevalence of PPCs was observed in the CT-defined emphysema group compared to the non-CT-defined emphysema group (19.6% vs. 7.8%, $P < 0.001$). Table 2 shows a multivariate logistic regression analysis for evaluating the impact of CT-defined emphysema on PPCs. After adjusting for age, sex, body mass index (BMI), smoking history, airway obstruction, surgical approach and extent of resection, CT-defined emphysema independently correlated with PPCs occurrence (adjusted odds ratio [OR], 2.35; 95% CI, 1.40–3.93; $P = 0.001$) in the entire cohort. Similar associations were observed among never-smokers (adjusted OR, 2.75; 95% CI, 1.39–5.44; $P = 0.004$).

CT-defined emphysema and prognosis

Kaplan–Meier curves showed that patients with CT-defined emphysema had a significantly worse OS compared to those without CT-defined emphysema (median OS, 8.77 years vs. Not reached; HR, 1.70; 95% CI, 1.18–2.44; $P = 0.001$), with a similar trend for DFS (median DFS, 5.41 vs. 7.24 years; HR, 1.46; 95% CI, 1.12–1.89;

Table 1 Characteristics of the patients with and without CT-defined emphysema

Patient characteristics	Total (*N* = 902)	Patients with CT-defined emphysema (*n* = 163)	Patients without CT-defined emphysema (*n* = 739)	*P* value
Age, year	61 (54, 67)	62 (55, 68)	60 (54, 67)	0.201
Sex, male	391(43.3%)	130(79.8%)	262(35.3%)	< 0.001
BMI, kg/m^2	24.4 (22.3,26.6)	23.5 (21.4,26.0)	24.6 (22.6,26.7)	< 0.001
Smoking status				< 0.001
Yes	275(30.5%)	91(55.8%)	184(24.9%)	
No	627(69.5%)	72 (44.2%)	555(75.1%)	
Pulmonary function test*				
FEV1,L	2.4(2.0,2.9)	2.5(2.0,3.0)	2.4(2.0,2.8)	0.581
FEV1/FVC	76.1(71.2,80.3)	73.1(66.4,78.4)	76.4(72.0,80.6)	< 0.001
FEV1/FVC < 0.7	169(20.2%)	50(33.8%)	119(17.2%)	< 0.001
DLCO/VA	1.4(1.3,1.6)	1.3(1.1,1.6)	1.5(1.3,1.6)	< 0.001
DLCO/VA pred %	95.8(84.7,108.5)	92.4(77.4,107.1)	96.3(85.6,108.6)	0.023
Tumor stage				0.039
I	597(66.2%)	94(57.7%)	503(68.1%)	
II	171(19.0%)	38(23.3%)	133(18.0%)	
IIIA	134(14.9%)	31(19.0%)	103(13.9%)	
Tumor				0.003
pT1	651(72.2%)	99 (60.7%)	552 (74.7%)	
pT2	195(21.6%)	48 (29.4%)	147 (19.9%)	
pT3	34(3.8%)	11 (6.7%)	23 (3.1%)	
pT4	22(2.4%)	5 (3.1%)	17 (2.3%)	
Node				0.405
pN0	675(74.8%)	116(71.2%)	559 (75.6%)	
pN1	112(12.4%)	24 (14.7%)	88 (11.9%)	
pN2	110(12.2%)	21 (12.9%)	89 (12.0%)	
pN3	5(0.6%)	2 (1.2%)	3 (0.4%)	
Predominant histologic patterns				
MIA	18(2.0%)	1(0.6%)	17(2.3%)	0.223
INMA				
Lepidic	144(16.0%)	18 (11.0%)	126 (17.1%)	0.058
Acinar	438(48.6%)	67(41.1%)	371 (50.2%)	0.035
Papillary	118(13.1%)	21(12.9%)	97 (13.1%)	0.934
Micropapillary	51(5.7%)	14(8.6%)	37(5.0%)	0.073
Solid	91(10.1%)	36 (22.1%)	55(7.4%)	< 0.001
IMA	42(4.7%)	6(3.7%)	36(4.9%)	0.514
Vascular invasion				0.004
Absent	701(77.7%)	113(69.3%)	588(79.6%)	
Present	201(22.3%)	50(30.7%)	151(20.4%)	
Pleural invasion				0.001
Absent	666(73.9%)	104(63.8%)	56,002(76.2%)	
Present	235(26.1%)	59(36.2%)	176(23.8%)	
EGFR gene				0.017
Wild	335(37.1%)	76(46.6%)	259(35.0%)	
Mutated	269(29.8%)	38(23.3%)	231(31.3%)	
NA	298(33.0%)	49(30.1%)	249(33.7%)	
KRAS gene				0.262
Wild	563(62.4%)	103(63.2%)	460(62.2%)	
Mutated	41(4.5%)	11(6.7%)	30(4.1%)	
NA	298(33.0%)	49(30.1%)	249(33.7%)	
ALK gene				0.630
Wild	571(63.3%)	107(65.5%)	464(62.8%)	
Rearranged	33(3.7%)	7(4.3%)	26(3.5%)	

Table 1 (continued)

Patient characteristics	Total (*N* = 902)	Patients with CT-defined emphysema (*n* = 163)	Patients without CT-defined emphysema (*n* = 739)	*P* value
NA	298(33.0%)	49(30.1%)	249(33.7%)	
Tumor location 1				0.636
Central	161(17.8%)	27(16.6%)	134(18.1%)	
Peripheral	741(82.2%)	136(83.4%)	605(81.9%)	
Tumor Location 2				0.986
Right lobe	565(62.6%)	102(62.6%)	463(62.7%)	
Left lobe	337(37.4%)	61(37.4%)	276(37.3%)	
Surgical approach				0.020
VATS	818(90.7%)	140(85.9%)	678(91.7%)	
Thoracotomy	84(9.3%)	23(14.1%)	61(8.3%)	
Extent of resection				0.311
Wedge resection	72(8.0%)	18(11.0%)	54(7.3%)	
Segmentectomy	10(1.1%)	1(0.6%)	9(1.2%)	
Lobectomy	814(90.2%)	144(88.3%)	670(90.7%)	
Pneumonectomy	6(0.7%)	0(0.0%)	6(0.8%)	
Length of stay, days				0.015
< 13	443(49.1%)	66(40.5%)	377(51.0%)	
≥ 13	459(50.9%)	97(59.5%)	362(49.0%)	
Adjuvant therapy				
Chemotherapy	324(35.9%)	77(47.2%)	247(33.4%)	0.001
TKI	125(13.9%)	14 (8.6%)	111 (15.0%)	0.031
Radiotherapy	41(4.5%)	11 (6.7%)	30 (4.1%)	0.136
Postoperative pulmonary complications	90(10.0%)	32(19.6%)	58(7.8%)	< 0.001
Type of postoperative pulmonary complication				
Prolonged air leak	16(1.8%)	7(4.3%)	9(1.2%)	0.007
Respiratory failure	6(0.7%)	3(1.8%)	3(0.4%)	0.041
Pneumonia	15(1.7%)	5(3.1%)	10(1.4%)	0.121
Pneumothorax	14(1.6%)	6(3.7%)	8(1.1%)	0.015
Severe atelectasis	12(1.3%)	4(2.5%)	8(1.1%)	0.167
Pleural effusion	41(4.5%)	9(5.5%)	32(4.3%)	0.509

Data are presented as median (interquartile range) for continuous variables, counts (proportions) for categorical variables

Abbreviations: CT = computed tomography; BMI = body mass index; VTE = venous thrombosis embolism; FVC = forced vital capacity; FEV1 = forced expiratory volume; RV = residual volume; TLC = total lung capacity; DLCO = diffusing capacity of the lungs for carbon monoxide; VA = alveolar volume; MIA = minimally invasive adenocarcinoma; INMA = invasive nonmucinous adenocarcinoma; IMA = invasive mucinous adenocarcinoma; NA = not available; EGFR = epidermic growth factor receptor; KRAS = kirsten rat sarcoma viral oncogene; ALK = anaplastic lymphoma kinase; VATS = video-assisted thoracoscopic surgery; TKI = tyrosine kinase inhibitors

P = 0.001) (Fig. 3a and e-Fig. 1a). The five-year OS rates of patients with and without CT-defined emphysema were 73.1% (95%CI: 66.1-80.9%) and 82.1% (95%CI: 79.1-85.2%), respectively (*P* = 0.006). However, no relationship between airway obstruction on spirometry and prognosis was observed (e-fig. 2). Multivariate Cox analyses were conducted to assess CT-defined emphysema after adjusting for potential risk factors related to DFS and OS in the study patients, including age, sex, BMI, smoking history, tumour stage, vascular invasion, pleural invasion, surgical approach, extent of resection, and airway obstruction (Table 3 and e-Table 3). In the adjusted analysis, the presence of CT-defined emphysema (adjusted HR, 1.44; 95% CI, 1.05–1.97; *P* = 0.022), along with tumour stage, vascular invasion, and pleural invasion, were significantly associated with OS. For DFS, the association with CT-defined emphysema weakened in magnitude after adjusting for potential risk factors and was not statistically significant (adjusted HR, 1.27; 95% CI, 0.97–1.66; *P* = 0.078) (e-Table 3).

For patients with CT-defined emphysema, the mild (LAA% ≤ 9%) and moderate–severe groups (LAA% > 9%) displayed no significant difference in DFS and OS (e-Fig. 4a and b). Using the established cutoff from our previous study [12], CLE with LAA% >17% was associated with mortality, but this association was not statistically significant (HR, 1.17; 95% CI, 0.68-2.00; *P* = 0.881) (e-Fig. 4c).

CT-defined emphysema in smokers and never-smokers

Considering the confounding effects of smoking on emphysema and lung cancer, we stratified the patients

Table 2 Logistic regression analysis for factors related to PPCs in the entire cohort and never-smokers

Characteristics	The entire cohort				Never-smokers			
	Univariate analysis	*P* value	Multivariate analysis	*P* value*	Univariable analysis	*P* value	Multivariate analysis	*P* value#
Age, year	1.00(0.98–1.03)	0.572			0.99(0.96–1.02)	0.469		
Sex, male	1.92(1.24–2.98)	0.004	1.40(0.82–2.37)	0.213	1.59(0.89–2.84)	0.120		
BMI, kg/m^2	0.99(0.92–1.05)	0.661			1.02(0.94–1.12)	0.646		
Smoking history								
Never smoker	Reference				-	-		
Former or current smoker	1.60(1.02–2.50)	0.040	1.07(0.63–1.80)	0.804	-	-		
CT-defined emphysema								
No	Reference		Reference		Reference		Reference	
Yes	2.87(1.79–4.59)	< 0.001	2.33 (1.38–3.91)	0.001	2.76(1.40–5.45)	0.003	2.75(1.39–5.44)	0.004
Airway obstruction								
No	Reference				Reference			
Yes	1.16(0.67–1.99)	0.596			0.89(0.39–2.05)	0.792		
Surgical approach								
VATS	Reference		Reference		Reference		Reference	
Thoracotomy	2.37(1.31–4.29)	0.005	2.12 (1.16–3.91)	0.015	1.99(0.89–4.74)	0.095	1.98(0.87–4.47)	0.103
Extent of resection								
Wedge resection	Reference				Reference			
Segmentectomy	-	0.999			-	0.999		
Lobectomy	0.88(0.41–1.91)	0.754			1.04(0.36–3.02)	0.943		
Pneumonectomy	1.60(0.17–15.48)	0.685			-	0.999		

Abbreviations: PPCs = postoperative pulmonary complications; CT = computed tomography; LAA = low-attenuation areas; OR = odds ratio; CI = confidence interval; BMI = body mass index; VATS = video-assisted thoracoscopic surgery

*False discovery rate corrected *P* values in the entire cohort were as follows: sex, *P* = 0.284; smoking history, *P* = 0.804; CT-defined emphysema, *P* = 0.004; and surgical approach, *P* = 0.030

#False discovery rate corrected *P* values in never-smokers were as follows: CT-defined emphysema *P* = 0.008; and surgical approach, *P* = 0.103

by smoking status. The patients with CT-defined emphysema showed worse survival than those without, regardless of smoking status (log-rank $P < 0.001$, Fig. 3b). When the analysis was limited to 627 never-smokers, the HR for CT-defined emphysema vs. non-CT-defined emphysema was 2.01 for OS (95% CI, 1.12–3.59, $P < 0.001$) (Fig. 3c). After adjusting for potential risk factors, the presence of CT-defined emphysema (adjusted HR, 1.71; 95% CI, 1.08–2.70; $P = 0.021$) remained an independent predictor of poor OS (Table 3).

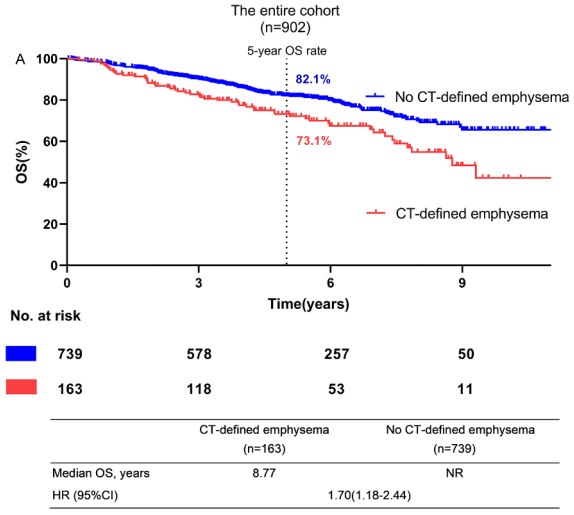
We further performed an exploratory analysis, including only never-smokers without spirometric obstruction. The analysis revealed that 838 out of 902 patients had available spirometry data, and 79.5% (669 out of 838) had normal spirometry. Additionally, there were 449 never-smokers with normal spirometry. Likewise, the presence of CT-defined emphysema was associated with an increased likelihood of poor prognosis (median DFS, 4.25 vs. 7.36 years; HR, 1.61; 95% CI, 1.01–2.56; $P = 0.015$; median OS, NR vs. NR; HR, 2.12; 95% CI, 1.06–4.23; $P < 0.001$) (e-Fig. 5).

CT-defined emphysema with histopathological evidence

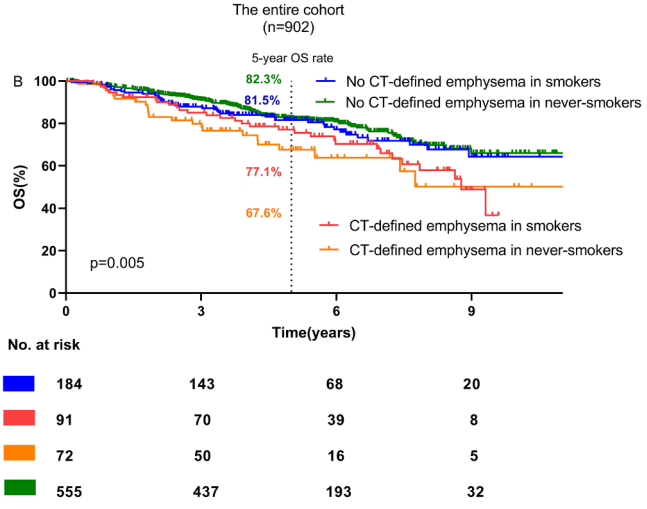
Among patients with CT-defined emphysema, 86.5% (141/163) were confirmed with histopathological evidence, showing high concordance between radiological and pathological emphysema. The patients who were confirmed to have CT-defined emphysema and with evidence of pathology showed higher occurrence rate of PPCs (adjusted OR, 2.08; 95% CI, 1.16–3.72; $P = 0.014$, e-Table 4) and the worst survival outcomes (log-rank $P < 0.001$, Fig. 4).

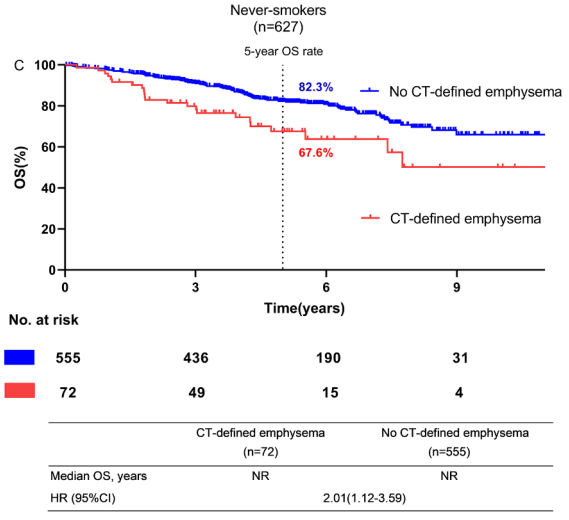
Stratified analysis

E-Figure 3 shows the stratified analysis for OS in the prespecified subgroups, including sex, age, BMI, smoking history, EGFR mutations/anaplastic lymphoma kinase rearrangements, year of diagnosis, and tyrosine kinase inhibitor (TKI) administration. The negative impact of CT-defined emphysema on survival was homogeneous in clinical and molecular subgroups, except for patients who were older than 65 years, had higher BMI (BMI ≥ 24), were former or current smokers, and those who received TKI as adjuvant treatment.



	CT-defined emphysema (n=163)	No CT-defined emphysema (n=739)
Median OS, years	8.77	NR
HR (95%CI)	1.70(1.18-2.44)	





	CT-defined emphysema (n=72)	No CT-defined emphysema (n=555)
Median OS, years	NR	NR
HR (95%CI)	2.01(1.12-3.59)	

Fig. 3 **A**) Kaplan-Meier survival plot for OS analysis in the entire cohort according to the presence of CT-defined emphysema. **B**) Kaplan-Meier survival plot for OS analysis of the smokers and never-smokers according to the presence of CT-defined emphysema. **C**) Kaplan-Meier survival plot for OS analysis of the never-smokers according to the presence of CT-defined emphysema. Abbreviations: CT = computed tomography; OS = overall survival; NR = not reached

Table 3 Cox regression analysis of CT-defined emphysema on overall survival in the entire cohort and never-smokers

Characteristics	The entire cohort				Never-smokers			
	Univariate analysis	*P* value	Multivariate analysis	*P* value*	Univariate analysis	*P* value	Multivariate analysis	*P* value#
Age(year)								
< 65	Reference				Reference			
≥ 65	1.00(0.74–1.36)	0.979			1.11(0.76–1.61)	0.605		
Sex, male	1.26(0.96–1.67)	0.095			1.17(0.80–1.70)	0.416		
BMI(kg/m^2)								
< 24	Reference				Reference			
≥ 24	1.01(0.76–1.34)	0.952			1.18(0.83–1.69)	0.354		
Smoking history								
Never smoker	Reference				-	-		
Former or current smoker	1.19(0.89–1.58)	0.244			-	-		
Tumor stage								
I	Reference		Reference		Reference		Reference	
II	1.99(1.41,2.83)	< 0.001	1.95(1.40–2.73)	< 0.001	2.47(1.64–3.74)	< 0.001	2.01(1.32,3.07)	0.001
IIIA	2.20(1.51,3.21)	< 0.001	2.12(1.48–3.02)	< 0.001	2.92(1.92–4.46)	< 0.001	2.00(1.28,3.12)	0.002
Extent of resection								
Wedge resection	Reference				Reference			
Segmentectomy	0.45(0.06–3.36)	0.437			0.50(0.07–3.77)	0.499		
Lobectomy	0.82(0.52–1.30)	0.824			0.67(0.39–1.15)	0.144		
Pneumonectomy	1.55(0.36–6.63)	0.553			2.80(0.64–12.37)	0.174		
Vascular invasion								
Absent	Reference		Reference		Reference		Reference	
Present	2.89(2.18–3.83)	< 0.001	1.87(1.37–2.56)	< 0.001	3.14(2.21–4.48)	< 0.001	1.98(1.33–2.94)	0.001
Pleural invasion								
Absent	Reference		Reference		Reference		Reference	
Present	2.80(2.12–3.69)	< 0.001	1.75(1.28–2.40)	< 0.001	3.30(2.27–4.53)	< 0.001	1.97(1.33–2.93)	< 0.001
Airway obstruction								
No	Reference				Reference			
Yes	1.15(0.82–1.62)	0.426			0.96(0.57–1.60)	0.862		
CT-defined emphysema								
No	Reference		Reference		Reference		Reference	
Yes	1.70(1.18–2.44)	0.001	1.44(1.05–1.97)	0.022	2.01(1.12–3.59)	0.003	1.71(1.08–2.70)	0.021

Abbreviations: CT = computed tomography; HR = hazard ratio; CI = confidence interval; BMI = body mass index; FVC = forced vital capacity; FEV1 = forced expiratory volume

*False discovery rate corrected *P* values in the entire cohort were as follows: TNM stage II, $P < 0.001$; TNM stage IIIA, $P < 0.001$; vascular invasion, $P < 0.001$; pleural invasion, $P < 0.001$; and CT-defined emphysema, $P = 0.022$

#False discovery rate corrected *P* values in never-smokers were as follows: TNM stage II, $P = 0.002$; TNM stage IIIA, $P = 0.003$; vascular invasion, $P = 0.002$; pleural invasion, $P = 0.002$; and CT-defined emphysema, $P = 0.021$

Propensity score matching analysis

After 1:2 PSM, a total of 424 patients were matched in both the CT-defined emphysema group ($n = 152$) and non-CT defined emphysema groups ($n = 272$). A balance check before and after PSM by reporting SMDs was shown in the e-Table 5. Patients with CT-defined emphysema still exhibited higher occurrence rate of PPCs (adjusted OR, 1.78; 95% CI, 1.03–3.07, $P = 0.040$, e-Table 6) and increased risk of poor OS compared to patients without CT-defined emphysema (adjusted HR, 1.50; 95% CI, 1.07–2.11; $P = 0.019$, e-Table 7) after adjusting for potential factors.

Discussion

In this longitudinal cohort study, we demonstrated that CT-defined emphysema has high consistence with pathological emphysema, while relatively weak association with spirometric airway obstruction. More importantly, CT-defined emphysema remained a strong predictor of PPCs and poor prognosis in patients with resectable LUAD, independently of airway obstruction.

By combining both radiological and pathological features of emphysema, the study provides comprehensive insights into how CT-defined emphysema affects patient outcomes during a 10-year follow-up period. Table 4 summarised studies that assessed prognostic value of CT-defined emphysema in patients with lung cancer. Few

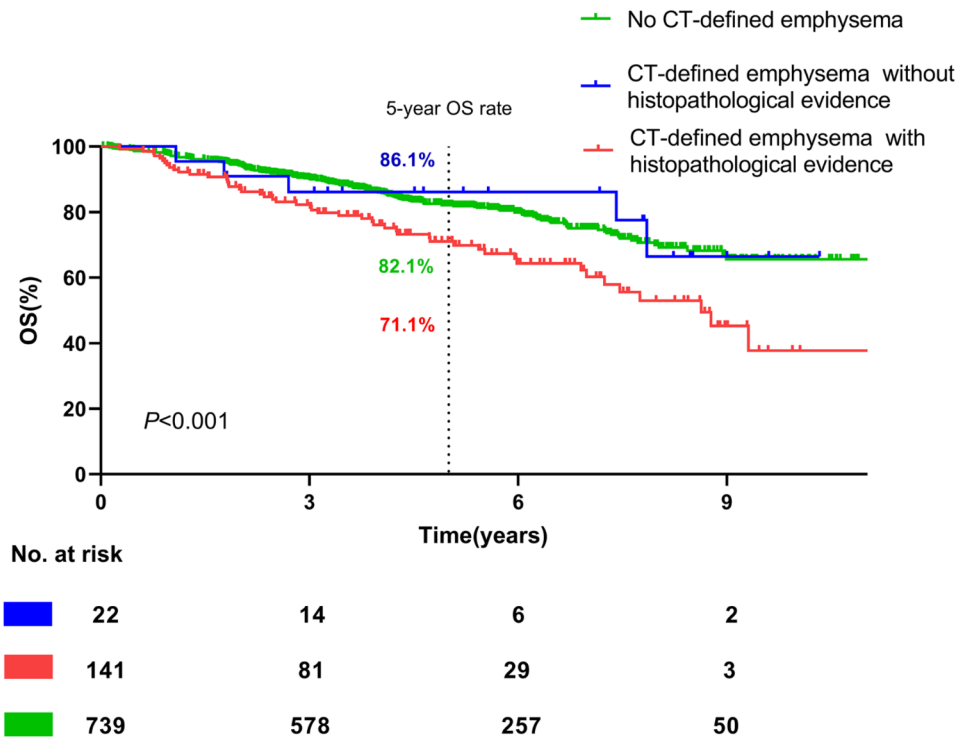


Fig. 4 Kaplan-Meier survival plot for OS analysis of the patients according to the presence of CT-defined emphysema and histopathological evidence. Abbreviations: CT = computed tomography; OS = overall survival

Table 4 Summaries of studies that assessed prognostic value of CT-defined emphysema in patients with lung cancer

Study	Country	Enrolled patients	Histological types	TNM stage	The percentage of never-smokers	Assessment Method of CT-defined emphysema	Matched histological features	Airway obstruction	PPCs
Ueda et al.7	Japan	100	NSCLC	I	0.0%	Quantitative	No	Yes	No
Gullón et al.8	Spain	353	NSCLC	I-IV	10.8%	Quantitative	No	Yes	No
Bishawi et al.9	USA	153	NSCLC	I	45.1%	Visual	No	No	No
Yasuura et al.10	Japan	1062	NSCLC	I-II	NA*	Quantitative	No	Yes	No
Colombi et al.11	Italy	75	NSCLC	I-III	19.0%	Quantitative	No	Yes	No
Ishida et al.13	Japan	721	NSCLC	I	NA*	Visual	No	No	Yes
Zhang et al.12	China	854	NSCLC	I-IV	54.8%	Visual+ Quantitative	No	Yes	No
Current Study	China	902	LUAD	I-III	69.5%	Visual+ Quantitative	Yes	Yes	Yes

Abbreviations: CT = computed tomography; NA = Not available; PPCs = postoperative pulmonary complications. *Only pack-years of smoking but not the smoking status was reported in the studies

studies have primarily focused on radiological diagnosis of emphysema with histopathological evidence [7–13]. High concordance (86.5%) between CT-defined emphysema and histopathologically matched abnormalities was observed in our study. The use of histopathological evidence to confirm CT findings lends additional robustness to the results, offering a more nuanced understanding of the correlation between radiological and pathological emphysema in LUAD patients. Additionally, the presence of CT-defined emphysema was reported to have an incidence of 18.1% in our study, which is lower than the rate among smokers (ranging from 32.3–58.0%) [6, 7, 22, 26]. This is reasonable because the most common cause of emphysema is cigarette smoking.

In our multivariable models that simultaneously included CT-defined emphysema and spirometric airway obstruction, only emphysema adversely affected survival. Lung cancers originating from emphysematous lung tissues exhibited aggressive pathological features, such as higher pathological stage, wild-type EGFR, vascular invasion, and pleural invasion, as previously reported [12, 13, 27]. We first observed that high-grade histological

patterns, including micropapillary and solid subtypes, were more common in the CT-defined emphysema group. An emphysematous background may provide an environment that results in more genetically heterogeneous and unstable tumours, leading to the development of high-grade lung cancer malignancies [13, 27]. From a histopathological perspective, alveolar type 2 cells (AT2s) are considered precursors of LUAD and pathogenic activators of emphysema [28, 29]. Boo et al. demonstrated that tobacco carcinogens might induce sustained insulin-like growth factor 2 (IGF2) -Wnt signalling activation through DNMT3A-mediated epigenetic control of IGF2 expression in AT2s during the development of pulmonary emphysema and lung cancer in smokers [30, 31]. B-cell activation and proliferation, along with increased antibody production, were observed within lymphoid follicles from chronic obstructive pulmonary disease (COPD) patients with emphysema, independent of the degree of airflow limitation [32]. A spatial landscape of tumour-infiltrating B- and plasma cells in early-stage LUAD revealed that memory B- and IgA + plasma cells may negatively correlate with cytotoxic T-cells, indicating their immunosuppressive potential [33]. These results suggest possible co-association relationships and crosstalk between emphysema and worse prognosis in LUADs.

Never-smokers are often underrepresented in lung cancer research. Compared with ever-smokers, some differences in physiological and radiographical characteristics exist in never-smokers [16, 34–37]. Our findings corroborate and extend the results of previous studies that have established the clinical impact of visually evident emphysema on CT in smokers with NSCLC [7]. The negative impact remained significant in never-smokers with LUAD, suggesting that lung cancer patients could be also susceptible to non-smoking risk factors associated with CT-defined emphysema. A similar trend was also observed in ever-smokers but without statistical significance. We speculate that smoking-induced cardiovascular or other diseases may interfere with the harmful effects of CT-defined emphysema.

CT-defined emphysema is a risk factor for developing PPCs in patients with LUAD, consistent with the previous evidence [13, 38, 39]. Prolonged air leak was the one of major events in our cohort as PPC. In our center, the combination of mechanical staplers and manual suturing would be used to avoid bleeding and air leaks. If potential air leakage occurs intraoperatively, various reinforcement measures, such as patches, biological glue, or direct electrocautery and suturing repair, were addressed to repair promptly. Postoperatively, chest tube drainage is used to monitor for air leakage, and if necessary, further exploration and muscle or pleural flap coverage would be performed. Emphysema predisposes the surrounding lung tissue to be more easily damaged during surgery, requiring longer recovery times.

However, evidence regarding the optimal surgical approach for lung cancer patients with CT-defined emphysema remains limited. According to NCCN guidelines, anatomic pulmonary resection is generally preferred for most patients with NSCLC. Segmentectomy or wedge resection is recommended for patients with limited pulmonary reserve or significant comorbidities that contraindicates lobectomy. In lung cancer patients with CT-defined emphysema, surgical procedures should balance oncological radicality with the preservation of postoperative lung function. JCOG0802/WJOG4607L trials revealed the non-inferiority of segmentectomy compared to lobectomy in terms of overall survival for patients with small-peripheral NSCLC [40]. Segmentectomy preserves lung function more effectively; however, it is associated with a higher locoregional recurrence rate. The CALGB 140,503 trial confirmed the non-inferiority of sublobar resection (wedge resection or segmentectomy) compared to lobectomy for peripheral stage IA NSCLC (≤ 2 cm) [41]. Miura et al. identified lobectomy as an independent risk factor for postoperative respiratory complications in patients with primary or metastatic lung cancer with emphysematous lungs [42]. The majority of patients in the cohort (90.2%) underwent lobectomy, making it challenging to determine how the choice of surgical procedure was influenced by clinical factors based on our study results. Overall, it can be inferred that sublobar resection might be suitable for patients with small-peripheral NSCLC with CT-defined emphysema. Future prospective studies are warranted to identify the optimal surgical approach for the specific population.

To avoid false positive findings of emphysema in patients with cystic lung diseases by AI analysis [43], we first assessed the presence of CT-defined emphysema visually and then evaluated the emphysema severity using an AI software. Visual assessment of CT scans remains important to describe distinct subtypes of emphysema and provides information about emphysema distribution [24]. CLE with LAA% >17% displayed poorer survival, but the LAA% cut-off needs to be interpreted cautiously. The LAA% threshold has not yet been extensively validated clinically. Baraghoshi et al. evaluated emphysema progression based on a COPD gene study with over 10 years of follow-up and highlighted the need to adjust CT technical characteristics [44]. We should strengthen the collaboration between engineers and doctors to standardize biomedical imaging techniques. Further, multicenter studies were needed to validate the effectiveness of the threshold, thereby providing more applicability for clinical practice.

CT-defined emphysema could serve as a marker for increased risk of PPCs and worse prognosis in resectable

LUAD. However, the management lacks standardized guidelines for this population. It is essential to integrate respiratory medicine, thoracic surgery, oncology, radiology, and other specialties to optimize individualized treatment decisions, including preoperative assessments, surgical approach choices, pulmonary rehabilitation, nutritional management, and inhalation therapy. In the future, we would combine genomics, metabolomics, and other multi-omics technologies to develop precision medicine strategies for lung cancer with CT-defined emphysema.

Limitations

Potential limitations should be acknowledged to fully appreciate the results of our study. First, this retrospective analysis is subject to selection bias because of study design, but we adopted several statistical analysis to enhance the robustness of the results. Second, the lack of longitudinal severity assessment of CT-defined emphysema makes clarifying the associations between emphysema progression and cancer development difficult. Third, we did not review the postoperative pathology specimens of patients without CT-defined emphysema to verify the presence of pathological emphysema. This may underestimate the incidence of pathological emphysema.

Conclusions

The presence of radiological and pathological emphysema predicts the occurrence of PPCs and long-term poor prognosis in resectable LUAD up to 10-years of follow-up, independently of airway obstruction. The adverse impact of emphysema on outcome of surgical treatment warrants further studies to establish optimal surveillance and treatment strategies for LAUD patients with CT-defined emphysema.

Abbreviations

AI	Artificial intelligence
ALK	Anaplastic lymphoma kinase
AT2s	Alveolar type 2 cells
BMI	Body mass index
CIs	Confidence intervals
CLE	Centrilobular emphysema
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DFS	Disease-free survival
DLCO	Diffusing capacity of the lungs for carbon monoxide
EGFR	Epidermal growth factor receptor
FDR	False discovery rate
FEV1/FVC	Forced expiratory volume in one second per forced vital capacity
HRCT	High-resolution computed tomography
IGF2	Insulin-like growth factor 2
IMA	Invasive mucinous adenocarcinoma
INMA	Invasive nonmucinous adenocarcinom
IQRs	Interquartile ranges
KRAS	Kirsten rat sarcoma viral oncogene
LUAD	Lung adenocarcinoma
MIA	Minimally invasive adenocarcinoma
NA	Not available
NR	Not reached
NSCLC	Non-small cell lung cancer
OR	Odds ratio
OS	Overall survival
PPCs	Postoperative pulmonary complications
PSE	Paraseptal emphysema
RV	Residual volume
SMD	Standardized mean differences
TLC	Total lung capacity
TKI	Tyrosine kinase inhibitors
TNM	Tumour, nodes and metastasis
VA	Alveolar volume
VATS	Video-assisted thoracoscopic surgery
VTE	Venous thrombosis embolism
%LAAs	Low attenuation areas

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-025-03225-6.

Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions

YXZ and YHZ designed the study and drafted the manuscript. YXZ and LL collected data, conducted data analyses and summarized the results in tables and figures. KWH, JWY, YY contributed to the data curation. XL, XJG, BH supervised data collection. BH, XL and YHZ critically edited the manuscript. YHZ is responsible for the overall content as a guarantor. All authors contributed to the interpretation of the results and revision of the manuscript for important intellectual content and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Permission for data analysis was granted by the Ethics Committee of the Beijing Chao-Yang Hospital, Beijing Institute of Respiratory Medicine, Capital Medical University, Beijing, China (No. 2024-ke-412 and No. 2021-ke-443). The requirement for obtaining informed consent was waived because of the retrospective study design nature. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Pulmonary and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
[2]Department of Radiology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

[3]Department of Thoracic Surgery, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
[4]Department of Pathology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

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