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Original Article

CT-defined Emphysema Morphology as a Predictor for Histological Subtypes of Lung Cancer: A Single-center Retrospective Study

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ABSTRACT

OBJECTIVE: Lung cancer and pulmonary emphysema share common risk factors and pathophysiological pathways. Emerging evidence suggests that emphysema morphology, rather than emphysema burden, may influence lung cancer histology. This study evaluated the association between computed tomography (CT)-defined emphysema characteristics and histological subtypes of lung cancer.

MATERIAL AND METHODS: A retrospective observational cohort study was conducted that included 144 patients with histologically confirmed lung cancer who underwent diagnostic thoracic CT between January 2020 and June 2024 at Dr. Saiful Anwar General Hospital in Indonesia. Emphysema morphology was visually classified as centrilobular emphysema (CLE), paraseptal emphysema, or mixed, and emphysema volume was quantified using 3D Slicer software. Associations with histological subtypes were analyzed using bivariate analyses and multivariate logistic regression, adjusted for age, sex, tumor size, and tumor location. Model performance was assessed using receiver operating characteristic analysis.

RESULTS: Adenocarcinoma (ADC) was the most common subtype (65.3%). Emphysema was present in 37.5% of patients and occurred more frequently in non-ADC subtypes. Emphysema morphology was significantly associated with histological subtype ($P < 0.001$). Multivariate analysis identified CLE as an independent predictor of ADC (adjusted odds ratio: 8.5; 95% confidence interval: 1.24–57.9; $P = 0.029$), and CLE remained significant after adjustment for tumor size and tumor location. The model demonstrated excellent discrimination (area under the curve: 0.89). Emphysema volume did not differ significantly between groups ($P = 0.339$).

CONCLUSION: CT-defined CLE is independently associated with lung ADC, whereas emphysema volume is not predictive of lung ADC. Emphysema morphology may serve as a non-invasive imaging biomarker to support histological risk stratification when tissue diagnosis is limited.

KEYWORDS: Lung cancer, adenocarcinoma, emphysema morphology, CT scan, biomarker

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INTRODUCTION

Lung cancer remains the most commonly diagnosed cancer worldwide, accounting for 12.4% of all cancer cases according to the latest GLOBOCAN 2022 data, and contributing to approximately 1.8 million deaths, or 18.7% of total cancer mortality. In Indonesia, lung cancer accounts for 12.6% of all cancer-related deaths, making it the leading cause of cancer mortality and the fourth most common cancer overall, after breast, cervical, and colorectal cancers. The annual incidence is projected to almost double from 30,023 cases in 2018 to 54,983 cases by 2040.[1-3]

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Lung cancer is broadly classified as small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC), with the latter accounting for approximately 85% of cases. According to the 2015 World Health Organization classification, the main NSCLC subtypes are adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell carcinoma, with ADC the most prevalent, comprising about 40% of NSCLC cases globally in 2022.[4-6]

Over the last decade, advances in molecularly targeted therapies have increased the importance of accurate histologic and genotypic classification of NSCLC. However, some conditions, such as clinical contraindications in patients with lung cancer, may make it impossible to perform invasive procedures, thereby delaying histologic diagnosis.[7]

Emphysema and lung cancer share common risk factors, inflammatory pathways, and molecular pathophysiology. Emerging evidence suggests that emphysema may serve as an independent risk factor for lung cancer; this is supported by several studies reporting that ADC is the histologic subtype of lung cancer most frequently associated with emphysema on CT.[8,9] Nevertheless, the relationship between emphysema characteristics and lung cancer histology and genotype remains unclear. This study aims to further explore and strengthen the evidence linking emphysema characteristics with lung cancer subtypes, potentially aiding in non-invasive diagnosis for biopsy-contraindicated patients and informing personalized screening protocols for high-risk populations.

MATERIAL AND METHODS

Study Population

This retrospective observational cohort study was conducted at Dr. Saiful Anwar General Hospital, East Java, Indonesia. All patients included in this study had primary lung cancer confirmed by histopathologic examination and had undergone diagnostic thoracic computed tomography (CT) scans between January 2020 and June 2024. CT images obtained before patients received cancer treatment were evaluated. Histopathologic examinations included both small (core needle and transbronchial biopsies) and large (surgical biopsies) specimens, which were evaluated by board-certified pathologists. Exclusion criteria were as follows: (1) patients with incomplete imaging data or poor CT image quality precluding emphysema assessment; (2) patients with secondary lung cancer and coexistence of other primary cancers; (3) patients with concomitant lung diseases, such as interstitial lung disease, that could confound emphysema interpretation. A total of 144 patients who met these criteria were enrolled by total sampling from the hospital's radiology and pathology archives. Ethical approval was granted by the Ethics Committee of Dr. Saiful Anwar General Hospital (approval no: 400/277/K.3/302/2023, approved on December 04, 2023).

Main Points

- Centrilobular emphysema (CLE) morphology on computed tomography is strongly and independently associated with the adenocarcinoma (ADC) subtype of lung cancer.
- Emphysema volume did not differ significantly between the ADC and non-ADC groups, suggesting that morphology is a more relevant predictor.
- CLE demonstrated excellent predictive performance for ADC, even after adjustment for tumor size and tumor location, with receiver operating characteristic curve analysis yielding an area under the curve of 0.89.
- Emphysema morphology may serve as a simple, non-invasive imaging biomarker to support histological prediction, especially when invasive biopsy is contraindicated.
- The predictive value of emphysema morphology could be further improved when integrated with additional radiologic features of the primary lung mass.

Tumor Size and Location Assessment

Tumor size was categorized according to the tumor–node–metastasis staging system as ≤5 cm (T1–T2) and >5 cm (T3–T4), based on established clinical prognostic thresholds that reflect differences in tumor burden and potential biological behavior.[10] Tumor location on CT images was classified as central or peripheral using radiologic criteria from previous studies. A tumor was defined as central if the lesion involved the main, lobar, or segmental bronchi or if the tumor epicenter was located within the inner one-third of the lung parenchyma. Tumors were classified as peripheral when the epicenter was in the outer two-thirds of the lung parenchyma without central bronchial involvement. In cases of large tumors extending across both central and peripheral regions, classification was based on the tumor epicenter at the level of the largest axial diameter.[11,12]

Emphysema Assessment

Emphysema characteristics were assessed on high-resolution thoracic CT images acquired with a 128-slice Toshiba Aquilion scanner (model TSX-101A). The evaluation comprised two components: emphysema morphology and emphysema volume. Two experienced radiologists independently assessed emphysema morphology by visual analysis to evaluate interobserver reliability. Emphysema was classified by the Fleischner Society into three morphological subtypes: centrilobular emphysema (CLE), paraseptal emphysema (PSE), and mixed-type emphysema (defined by the coexistence of centrilobular and paraseptal features). Quantitative emphysema volume, expressed in cubic centimeters (cm^3), was measured with the open-source 3D Slicer software (version 5.6.2; https://www.slicer.org/), with segmentation techniques employed to identify low-attenuation areas with a threshold range of −950 to −1024 Hounsfield units.[13] The independent variables were emphysema morphology and emphysema volume; the dependent variable was the histological subtype of lung cancer (ADC, SCC, small cell carcinoma, and adenosquamous carcinoma).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 25. Descriptive statistics were employed to summarize patient characteristics, including means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. For statistical analysis, the chi-square

test was used to assess the association between emphysema morphology and histological subtypes of lung cancer. Independent t-tests were applied to compare emphysema volumes between groups. Multivariable logistic regression analysis was conducted to identify independent predictors of specific histological subtypes (e.g., ADC), adjusting for age, sex, emphysema morphology, tumor size, and tumor location. Receiver operating characteristic (ROC) curve analysis was subsequently performed using the multivariable logistic regression model to evaluate the discriminative performance of emphysema morphology in differentiating ADC from non-ADC histological subtypes, and the area under the curve (AUC) was reported. A *P* value of <0.05 was considered statistically significant. Interobserver agreement for emphysema morphology classification was evaluated using Cohen's kappa statistic.

RESULTS

A total of 144 lung cancer patients participated in this study. The average age of the patients was 59.58 years; 62 (43.1%) were under 60 years and 82 (56.9%) were 60 years or older. The sex distribution among the subjects was 91 males (63.2%) and 53 females (36.8%). Histopathological data showed that ADC was the most frequent lung cancer subtype, diagnosed in 94 patients (65.3%), followed by SCC (29 patients, 20.1%), small cell carcinoma (12 patients, 8.3%), and adenosquamous carcinoma (9 patients, 6.3%). All characteristics of the subjects are presented in Table 1. No significant differences in demographic variables were observed between histological subtypes.

Interobserver agreement analysis revealed substantial agreement between the two expert radiologists in the assessment of emphysema morphology, with a Cohen's kappa value of 0.71. This finding indicates good interobserver consistency in determining emphysema morphology.

In bivariate analysis, tumor size was significantly associated with histological subtype: non-ADC tumors more frequently presented as larger than 5 cm compared with ADC (*P* = 0.041). In contrast, tumor location (central vs. peripheral) did not show a significant association with histological subtype (*P* = 0.155).

Emphysema was detected on CT images in 54 patients (37.5%), whereas 90 patients (62.5%) showed no emphysematous changes. Emphysema prevalence differed significantly between histological groups, with a higher prevalence observed in the non-ADC group than in the ADC group (*P* < 0.05; Table 1). Among those with emphysema, CLE was present in 19 patients (35.2%), PSE in 10 patients (18.5%), and mixed-type emphysema in 25 patients (46.3%) (Table 2). Although overall emphysema prevalence was higher in the non-ADC group, subsequent analyses restricted to emphysema-positive patients demonstrated that emphysema morphology differed significantly by histological subtype.

In the restricted analysis of emphysema-positive patients, a significant association was observed between emphysema morphology and histological subtype of lung cancer (*P* < 0.001), with pairwise comparisons demonstrating a pronounced difference between centrilobular and mixed-emphysema types (*P* < 0.001) (Table 3). Multivariate logistic regression analysis identified CLE as an independent predictor of ADC, with an adjusted odds ratio (OR) of 8.5 [95% confidence interval (CI): 1.247–57.931; *P* = 0.029] (Table 4). This association remained significant after adjustment for age, sex, tumor size, and tumor location, none of which showed an independent association with ADC in the final model. ROC curve analysis based on the multivariable logistic regression model—including age, sex, emphysema morphology, tumor size, and tumor location—demonstrated excellent discrimination between ADC and non-ADC subtypes, with an AUC of 0.89 (95% CI: 0.801–0.987; *P* < 0.001) (Figure 1).

Meanwhile independent t-test analysis showed no significant difference between the mean emphysema volume in ADC (542.71±406.72 cm^3) compared with non-ADC patients (449.73±394.70 cm^3) (*P* = 0.339). The standard deviations in both groups were relatively large, suggesting considerable variability in emphysema volume among individuals. These findings imply that, within this study population, volumetric emphysema measurements did not differ meaningfully across the major histological subtypes of lung cancer.

Table 1. Patient characteristics and emphysema status

Characteristics	Total (n = 144)	Adenocarcinoma	Squamous cell carcinoma	Small cell carcinoma	Adenosquamous carcinoma	*P* value**
Age in years (mean ± SD)	59.58 ± 10.31					
<60	62 (43.1%)	41 (43.6%)	14 (48.3%)	4 (33.3%)	3 (33.3%)	0.992
≥60	82 (56.9%)	53 (56.4%)	15 (51.7%)	8 (66.7%)	6 (66.7%)	
Sex						
Male	91 (63.2%)	55 (58.5%)	20 (69%)	11 (91.7%)	5 (55.6%)	0.157
Female	53 (36.8%)	39 (41.5%)	9 (31%)	1 (8.3%)	4 (44.4%)	
Emphysema status						
Presence	54 (37.5%)	24 (27.1%)	18	8 (66.7%)	4 (44.4%)	<0.001*
Absent	90 (62.5%)	70 (72.9%)	11	4 (33.3%)	5 (55.6%)	

*Statistically significant
**Hypothetical analysis was measured using chi-square for adenocarcinoma vs. non-adenocarcinoma
SD: standard deviation

Table 2. Morphological characteristics and volume of emphysema according to lung cancer subtypes

Variable	Total (n = 54)	Lung cancer subtype		*P* value
		Adenocarcinoma	Non-adenocarcinoma	
Age in years (mean ± SD)	61.22±9.92			
<60	21 (38.9%)	8 (33.3%)	13 (43.3%)	0.453
≥60	33 (61.1%)	16 (66.7%)	17 (56.7%)	
Emphysema morphology				
Centrilobular	19 (35.2%)	17 (70.8%)	2 (6.7%)	<0.001*
Paraseptal	10 (18.5%)	5 (20.8%)	5 (16.7%)	
Mix	25 (46.3%)	2 (8.3%)	23 (76.7%)	
Tumor location				
Peripheral	13 (24.1%)	8 (33.3%)	5 (16.7%)	0.27
Central	41 (75.9%)	16 (66.7%)	25 (83.3%)	
Tumor size				
>5 cm	40 (74.1%)	14 (58.3%)	26 (86.7%)	0.041*
≤5 cm	14 (25.9%)	10 (41.7%)	4 (13.3%)	
Emphysema volume (cm^3) (mean ± SD)	491.06±399.05	542.71±406.72	449.73±394.70	0.339

*Statistically significant
SD: standard deviation

Table 3. Pairwise comparison between emphysema morphology subtype

Variable (n = 54)	*P* value <0.05
Emphysema morphology	
Centrilobular-paraseptal	0.132
Centrilobular-mixed type	<0.001*
Paraseptal-mixed type	0.076

*Statistically significant difference based on post-hoc pairwise comparison analysis ($P < 0.05$)

Table 4. Multiple logistic regression analysis of emphysema morphology and the risk of lung adenocarcinoma

Variable	Adjusted OR	B	95% CI	*P* value
Centrilobular emphysema	8.50	2.14	1.247–57.931	0.029
Mixed-type emphysema	0.08	-2.44	0.013–0.584	0.012

OR: odds ratio, CI: confidence interval

DISCUSSION

Our study provides compelling evidence that ADC is the predominant histological subtype of lung cancer, accounting for 65.3% of diagnosed lung malignancies. This finding aligns with well-documented global epidemiological trends that demonstrate a progressive increase in ADC incidence over recent decades, with ADC now representing approximately 40% of all lung cancers and 60% of non-small-cell lung cancer cases in Western populations.[6,14] Several factors may contribute to this epidemiological shift, including changing smoking patterns, such as increased use of filtered cigarettes leading to greater peripheral lung deposition of carcinogens, evolving histological classification systems, and improving detection of asymptomatic peripheral tumors through the widespread implementation of CT screening.[15] We observed a significantly higher prevalence of emphysema in the non-ADC group than in the ADC group. The strong correlation between smoking-related lung injury and specific histological subtypes, especially SCC and SCLC, may account for the higher prevalence of emphysema in the non-ADC group. The main risk factor for the development of emphysema—heavy tobacco exposure—is traditionally associated with these subtypes.[4,16] On the other hand, patients with lower cumulative smoking exposure or even those who have never smoked may develop ADC, which could account for the lower overall prevalence of emphysema in this population.[17] Importantly, this apparent discrepancy reflects differences in emphysema prevalence rather than in emphysema pattern, and the presence of emphysema alone does not sufficiently explain histological differences. In the present study, analyses of emphysema morphology were restricted to emphysema-positive patients, allowing a clear distinction between emphysema presence and emphysema morphology. Crucially, results from this restricted emphysema-positive cohort indicate that emphysema morphology, particularly CLE, remains important in differentiating ADC from other histological subtypes, even though the presence

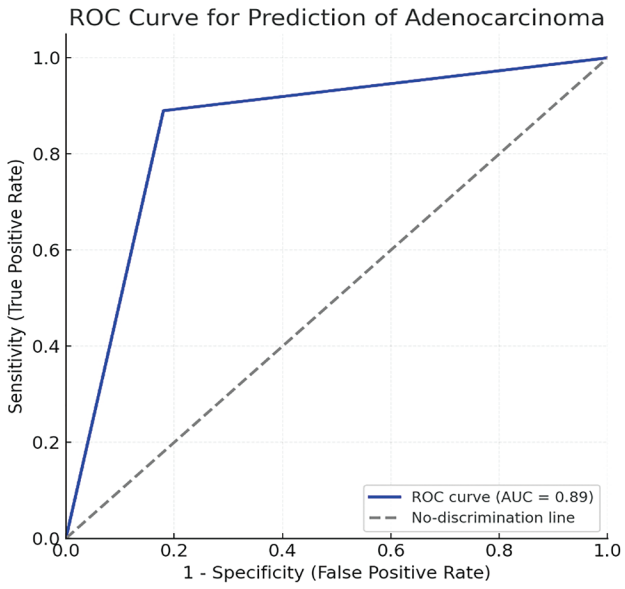

Figure 1. ROC curve for the logistic regression model predicting adenocarcinoma subtype based on emphysema morphology

ROC: receiver operating characteristic

of emphysema is more common in non-ADCs. Of particular clinical significance, our analysis revealed a robust and statistically significant association between CLE morphology and ADC histology (OR: 8.5, 95% CI: 1.247–57.93; $P = 0.029$). This finding corroborates and extends previous observations by Zhang et al.[18], who reported that 68.5% of lung cancer patients with radiologically confirmed emphysema presented with ADC, with CLE representing the predominant emphysema pattern (67% of cases). Even after adjustment for tumor size and location, CLE remained independently associated with ADC. This suggests that the observed relationship is not merely a reflection of tumor distribution or extent, but may instead indicate underlying pathophysiological mechanisms linking specific emphysema morphology to ADC development.

Tumor size and location were also investigated to further elucidate whether this association could be affected by tumor-related characteristics. Tumor size and histological subtype were significantly correlated in the bivariate analysis, but this correlation diminished after multivariate adjustment. This implies that rather than acting as a separate predictor of histological subtype, tumor size may reflect downstream effects of tumor growth dynamics and common etiologic factors. Conversely, emphysema morphology, especially CLE, remained independently associated with ADC, highlighting its potential role as a biologically significant imaging biomarker rather than as a proxy for tumor size.[9,19]

The pathophysiological mechanisms underlying the association between CLE and ADC likely involve complex interactions among chronic inflammation, protease-antiprotease imbalance, and hypoxia-mediated carcinogenesis. At the molecular level, the observed MMP-9/TGF-β1 imbalance in CLE patients may create a permissive microenvironment for ADC development through multiple pathways: (1) promotion of extracellular matrix degradation, facilitating tumor invasion, (2) activation of epithelial-mesenchymal transition programs, and (3) generation of reactive oxygen species leading to DNA damage and oncogenic mutations. Furthermore, the characteristic peripheral distribution of CLE lesions may preferentially expose the terminal bronchiolar and alveolar epithelium –the putative cells of origin for ADC– to sustained inflammatory insults and mitogenic stimuli.[16]

In contrast to the clear association between CLE and ADC, our analysis of PSE revealed more nuanced relationships with lung cancer subtypes. While PSE alone did not demonstrate statistically significant associations with specific histological patterns, we observed notable synergistic effects when PSE coexisted with CLE in non-ADC cases, particularly in SCC. This finding parallels recent work by Durawa et al.[20] demonstrating that combined PSE + CLE morphology, but not PSE in isolation, conferred a substantially elevated cancer risk (OR: 4.0).[19] The apparent subtype-specificity of these emphysema-cancer associations likely reflects fundamental differences in underlying molecular mechanisms: whereas CLE-associated ADC may develop through MMP-9 mediated pathways as discussed above, PSE's inhibition of MMP-2 could preferentially drive squamous carcinogenesis by altering tissue remodeling dynamics and disrupting normal epithelial differentiation programs.[16] Additionally, the coexistence of CLE and PSE may create a unique pulmonary microenvironment characterized by both proximal and distal airway injury, potentially explaining the observed association with SCC, which typically arises from more central bronchial epithelium.[21]

A particularly noteworthy finding from our study was the lack of significant correlation between quantitative emphysema volume measures and specific histological subtypes ($P = 0.339$). This observation, consistent with multiple previous investigations, strongly suggests that qualitative morphological characteristics of emphysema –rather than the disease burden alone– represent the critical determinants of subtype-specific cancer risk.[22,23] From a clinical perspective, this emphasizes the importance of detailed pattern analysis in the interpretation of thoracic imaging and suggests that current lung cancer screening protocols might benefit from incorporating assessments of emphysema morphology into risk-stratification algorithms.

The clinical implications of our findings are potentially substantial. The robust association between CLE morphology and ADC risk identifies a readily detectable imaging biomarker that could enhance early detection efforts, particularly in high-risk populations, such as current or former smokers. Furthermore, the distinct relationships between different emphysema patterns and specific cancer subtypes may eventually inform personalized surveillance strategies and even targeted prevention approaches. However, several important limitations must be acknowledged when interpreting these results. First, the retrospective study design inherently limits our ability to control for all potential confounding variables, particularly detailed smoking exposure measures, such as smoking status and cumulative pack-year history, which may influence both emphysema development and lung cancer histology. Consequently, the observed associations should be interpreted as associative rather than causal. Accordingly, despite good discriminative performance on ROC analysis, these findings

should be interpreted as exploratory and hypothesis-generating rather than as evidence of definitive clinical predictive utility. Second, while our sample size (n = 144) provides adequate power to detect major associations, rare histological subtypes (e.g., small cell carcinoma, adenosquamous carcinoma) were underrepresented, thereby limiting the statistical power for meaningful subgroup analyses. Third, the single-center nature of our study may limit generalizability to more diverse populations.

CONCLUSION

Future research should include prospective, multicenter studies that incorporate detailed environmental exposure data, molecular profiling of emphysematous lung tissue, and advanced imaging analytics to further elucidate the mechanisms linking specific emphysema patterns to lung cancer pathogenesis. Additionally, investigation of potential interactions between emphysema morphology and emerging biomarkers such as circulating tumor DNA or specific mutational signatures could yield valuable insights for precision prevention strategies.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Ethics Committee of Dr. Saiful Anwar General Hospital (approval no: 400/277/K.3/302/2023, approved on December 04, 2023).

Informed Consent: The requirement for informed consent was waived due to the retrospective design.

Footnotes

Authorship Contributions

Concept: F.A.A., D.R.E., S.D.P., N.S., Design: F.A.A., D.R.E., S.D.P., N.S., Data Collection or Processing: F.A.A., Analysis or Interpretation: F.A.A., D.R.E., S.D.P., N.S., Literature Search: F.A.A., Writing: F.A.A., D.R.E., S.D.P.

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