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ORIGINAL RESEARCH

Associations Between Morphological Phenotypes of COPD and Clinical Characteristics in Surgically Resected Patients with COPD and Concomitant Lung Cancer

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Purpose: The associations between morphological phenotypes of COPD based on the chest computed tomography (CT) findings and clinical characteristics in surgically resected patients with COPD and concomitant lung cancer are unclear. The purpose of this study was to clarify the differences in clinical characteristics and prognosis among morphological phenotypes based on the chest CT findings in these patients.

Patients and Methods: We retrospectively reviewed the medical records of 132 patients with COPD and concomitant lung cancer who had undergone pulmonary resection for primary lung cancer. According to the presence of emphysema and bronchial wall thickness on chest CT, patients were classified into three phenotypes: non-emphysema phenotype, emphysema phenotype, or mixed phenotype.

Results: The mixed phenotype was associated with poorer performance status, higher score on the modified British Medical Research Council (mMRC) dyspnea scale, higher residual volume in pulmonary function, and higher proportion of squamous cell carcinoma than the other phenotypes. Univariate and multivariate Cox proportional hazards regression analyses showed that the extent of emphysema on chest CT, presented as a low attenuation area (LAA) score, was an independent determinant that predicted prognosis. In the Kaplan-Meier analysis, the Log rank test showed significant differences in survival between the non-emphysema and mixed phenotypes, and between the emphysema and mixed phenotypes.

Conclusion: The cross-sectional pre-operative LAA score can predict the prognosis in surgically resected patients with COPD and concomitant lung cancer. The COPD phenotype with both emphysema and bronchial wall thickness on chest CT was associated with poorer performance status, greater extent of dyspnea, greater impairment of pulmonary function, and worse prognosis.

Keywords: LAA, emphysema, CT, prognosis, mortality, surgery

Introduction

There is growing recognition that chronic obstructive pulmonary disease (COPD) may influence lung cancer. Meta-analyses conducted to assess the impact of COPD on the overall survival (OS) of lung cancer patients have suggested that coexisting COPD is related to poor survival and disease-free survival outcomes.[1,2] In patients with a newly and pathologically confirmed diagnosis of lung cancer, COPD is significantly associated with decreased OS of lung cancer, and the OS of lung cancer gradually worsens with increased severity of COPD.[3] On the other hand, in patients with COPD undergoing lung cancer surgery, the presence of COPD itself does not influence long-term survival, although they are at greater risk of postoperative complications than patients with normal respiratory function.[4,5]

COPD can be classified into various morphological phenotypes based on the findings of chest computed tomography (CT) according to the presence of emphysema and/or airway wall thickness, and the morphological phenotypes of COPD

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present different clinical characteristics.[6–11] Wang et al revealed an association between the morphological phenotype of COPD and clinical characteristics in patients with COPD and concomitant lung cancer, suggesting that the emphysema-predominant phenotype of COPD, which is detected by a sharp "angle of collapse" in the maximum expiratory flow volume (MEFV) curve, is an independent prognostic risk factor for squamous carcinoma.[3] On the other hand, the cross-sectional area of the erector spinae muscles (ESM_{CSA}) obtained from a single-slice axial chest CT image correlates with the clinical parameters of COPD and may be the strongest risk factor for all-cause mortality in patients with COPD. In addition, the accelerated decline in ESM_{CSA} is related to frequent exacerbations and poor prognosis.[12,13]

However, the associations between morphological phenotypes of COPD based on the chest CT findings and clinical characteristics in surgically resected patients with COPD and concomitant lung cancer are unclear. Information on prognostic determinants and the association between ESM_{CSA} and clinical characteristics in these patients are lacking. In the present study, we sought to elucidate the differences in clinical characteristics including postoperative complications and prognosis among morphological phenotypes based on the chest CT findings in these patients in order to provide additional information for predicting all-cause mortality and considering whether early intensive therapeutic intervention for COPD and limited resection for primary lung cancer should be applied. One benefit of this study is easy applicability to clinical practice for understanding the clinical characteristics of these patients, because our methodology for classification of COPD into three phenotypes according to the CT findings is relatively easy.

Materials and Methods

Subjects and Protocols

This is a single-center retrospective cross-sectional study. We retrospectively reviewed the medical records of 132 patients with COPD and concomitant lung cancer who had undergone pulmonary resection for primary lung cancer at Shinshu University Hospital between April 2003 and October 2016. All patients underwent chest CT and pulmonary function tests before surgery. The date of the surgery was within 30 days of the CT scan and pulmonary function tests.

The diagnosis of COPD was based on the patients' clinical history and symptoms, including dyspnea on exertion and pulmonary function characterized by airflow obstruction ($FEV_1/FVC<70\%$ after inhalation of short-acting β_2-agonists) in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report.[15] All patients had a smoking history of more than 10 pack-years. Patients with emphysema and concomitant interstitial lung disease, which was termed combined pulmonary fibrosis and emphysema (CPFE), were excluded from the study, even if they had airflow obstruction. Patients with pulmonary complications such as asthma, diffuse panbronchiolitis, sinobronchitis, bronchiectasis, bronchiolitis obliterans, late sequelae of pulmonary tuberculosis, or severe cerebral-cardiovascular disease were also excluded from the study.

We obtained clinical data, including the results of preoperative pulmonary function tests and laboratory examinations, chest CT findings, the performance status evaluated using the Eastern Cooperative Oncology Group performance status score, the modified British Medical Research Council (mMRC) dyspnea scale, the pathological stage of lung cancer, postoperative complications, and survival. The tumor, nodes, and metastasis (TNM) stage was evaluated based on the 7th edition of the TMN classification of lung cancer.[14] Postoperative complications following pulmonary resection were defined as complications which occurred on postoperative days 0–30. The preoperative prognostic nutritional index (PNI),[16] neutrophil-to-lymphocyte ratio (NLR),[17] platelet-to-lymphocyte ratio (PLR),[18] Advanced Lung Cancer Inflammation Index (ALI),[19] modified Glasgow Prognostic Score (mGPS),[20] and prognostic index (PI),[21] which were previously reported to be prognostic determinants in lung cancer, were calculated based on laboratory data. All patients were observed until their death or the end of the study (October 1, 2021). The follow-up period was at least 5 years.

This study was approved by the institutional research ethics committee of Shinshu University School of Medicine, and all patients gave their written informed consent to participate (the approval number: 5394). This retrospective observational study protocols were performed in accordance with the principles outlined in the Declaration of Helsinki of the World Medical Association.

CT Assessment and Classification of COPD into Three Phenotypes

All patients underwent chest CT scans during an inspiratory breath-hold in the supine position before surgery. Images were reconstructed by using a standard reconstruction algorithm for the lung by using a slice thickness of 1.25 mm. A visual assessment of the CT scan for the extent of emphysema was performed based on our previous reports.[6,7,22,23] Briefly, emphysema was scored visually in the bilateral upper, middle, and lower lung fields according to the methods of Goddard et al.[24] The visual scores for low attenuation areas (LAAs) were calculated as the sum of scores for the six lung fields (score range: 0–24). To evaluate the degree of airway wall thickness, CT images were analyzed using an image-analyzing software (EV Insite®; PSP, Co., Tokyo, Japan). The cross-sectional airway wall areas of B1 and B10 (third-generation bronchi) in the right lung were measured by manual tracing and presented as percentage of airway wall area (WA%). The cut-off value of WA% of B1 and B10 for detecting apparent bronchial wall thickness evaluated using visual assessment was determined using receiver operating characteristic (ROC) curve analysis (areas under the ROC curve were 0.751 and 0.785, respectively). Consequently, we evaluated the WA% of B10 for detecting apparent bronchial wall thickness in the present study, because it had larger area under the ROC curve than the WA% of B1. The sensitivity and specificity were both 71.2% when the cut-off value for the WA% of B10 was 50.014%. Therefore, we defined WA% $\geq$ 50% for B10 as bronchial wall thickness. Following a method described in previous studies,[25,26] a quantitative analysis of the ESM_{CSA} was performed using an image-analyzing software (EV Insite®; PSP, Co., Tokyo, Japan). The chest CT images were reviewed by two expert pulmonologists (Y.S. and Y.K., 10 and 22 years of experience, respectively) blinded to the patients' clinical information.

The patients were classified into three phenotypes according to the CT findings: non-emphysema phenotype characterized by the absence of emphysema with LAA = 0 regardless of bronchial wall thickness; emphysema phenotype characterized by the presence of emphysema with LAA $\geq$ 1 without bronchial wall thickness; or mixed phenotype characterized by the combination of the presence of emphysema with LAA $\geq$ 1 and bronchial wall thickness.

Pulmonary Function Tests

All patients underwent spirometry and measurement of the lung diffusion capacity for carbon monoxide (DLco), the DLco corrected for alveolar volume (DLco/VA), the total lung capacity (TLC), the residual volume (RV), and the functional residual capacity (FRC) before surgery. Measurements were performed using a pulmonary function testing system (Chestac-8900®; CHEST Co., Ltd., Tokyo, Japan) as described previously.[6,7,22,23]

Statistical Analysis

A univariate Cox proportional hazards regression analysis followed by multivariate analysis was used to identify determinants associated with the risk of death. Variables associated with prognosis in COPD, such as age, body mass index (BMI), smoking index, extent of airflow obstruction (GOLD stage), extent of dyspnea (mMRC dyspnea scale), extent of emphysema (LAA) and ESM_{CSA}, were considered for inclusion in the analyses. Survival in each group was estimated using the Kaplan-Meier method, and differences between groups were compared using the Log rank test. Continuous variables were compared among three groups in a one-way analysis of variance, followed by Tukey–Kramer multiple comparisons correction. Two categorical variables such as gender and smoking status were compared among three groups using Fisher's exact test. All statistical analyses were performed using the StatFlex software program (version 7; Artech Co. Ltd, Osaka, Japan). $P<0.05$ was considered significant in all statistical analyses.

Results

A total of 1316 patients had undergone pulmonary resection for primary lung cancer at our institution during the study period, including 196 (14.9%) patients who were suspected of having COPD. Sixty-four of these patients were excluded from the study because they did not meet the criteria for COPD, had pulmonary complications other than COPD before surgery, or had insufficient data. The data on the remaining 132 patients were analyzed in this study.

Table 1 shows the baseline clinical characteristics of surgically resected patients with COPD and concomitant lung cancer. BMI was significantly higher in the non-emphysema phenotype than in the other phenotypes. The proportion of

Table 1 Baseline Clinical Characteristics of the Three Phenotypes in Surgically Resected Patients with COPD and Concomitant Lung Cancer

	All Subjects (n=132)	Non-Emphysema Phenotype (n=36)	Emphysema Phenotype (n=49)	Mixed Phenotype (n=47)
Age, years	70.50±7.93	71.86±6.10	69.67±8.99	70.32±8.03
Gender, female/male	7/125	4/32	1/48	2/45
BMI, kg/m^2	22.99±3.45	24.82±3.18	22.28±3.32 **	22.32±3.33 **
Smoking index, pack-years	61.28±36.38	51.87±42.91	66.56±32.85	60.11±36.31
Smoking status, Former/current smoker	85/47	28/8	24/25 *	33/14
GOLD stage, 1/2/3/4	66/58/8/0	24/12/0/0	24/24/1/0	18/22/7/0
PS	0.70±0.52	0.53±0.65	0.59±0.50	0.96±0.29 **††
mMRC dyspnea scale	1.02±0.69	0.81±0.71	0.94±0.69	1.26±0.64 **†
Chest CT findings				
LAA score	7.12±7.33	0±0	8.80±6.54 **	10.83±7.18 **
WA% of right B1, %	50.49±10.05	48.08±6.84	46.27±8.94	56.74±10.23 **††
WA% of right B10, %	48.90±7.68	47.50±6.95	43.12±4.67 **	56.00±4.46 **††
ESM_{CSA}, mm^2	3203.51±751.68	3236.52±742.26	3217.38±655.10	3163.77±859.88
Pulmonary function tests				
VC, L	3.52±0.73	3.46±0.66	3.74±0.72	3.37±0.76†
%VC, %	102.48±16.74	102.47±14.17	105.61±16.87	99.08±18.14
FVC, L	3.36±0.74	3.25±0.72	3.58±0.73	3.20±0.74†
%FVC, %	99.73±17.66	99.85±17.03	103.28±17.33	95.94±18.06
FEV_1, L	2.03±0.54	2.04±0.48	2.14±0.52	1.91±0.58
$\%FEV_1$, %	75.68±17.08	78.11±14.49	76.83±17.15	72.62±18.68
FEV_1/FVC, %	60.34±7.53	62.79±5.17	59.86±7.21	58.96±0.94
TLC, L	5.97±0.99	5.74±0.96	6.14±0.91	5.98±1.07
%TLC, %	114.63±15.14	112.97±14.61	115.50±13.41	115.03±17.35
RV, L	2.43±0.54	2.24±0.61	2.39±0.39	2.62±0.57 **
%RV, %	142.55±31.22	131.56±35.32	138.49±20.25	155.49±33.49 **†
FRC, L	3.58±0.76	3.28±0.71	3.67±0.74 *	3.71±0.76 *
%FRC, %	102.66±19.68	102.78±21.55	100.09±18.27	105.3±19.67
DLCO, mL/min/mmHg	16.67±5.30	20.07±4.02	15.41±4.65 **	15.36±5.73 **
%DLCO, %	69.97±21.49	85.90±15.62	63.62±18.71 **	64.28±22.16 **
DLCO/VA, mL/min/mmHg/L	3.75±1.26	4.68±0.97	3.40±1.09 **	3.39±1.27 **
%DLCO/VA, %	85.68±29.43	107.76±23.10	77.43±26.16 **	77.19±28.62 **

(*Continued*)

Table 1 (Continued).

	All Subjects (n=132)	Non-Emphysema Phenotype (n=36)	Emphysema Phenotype (n=49)	Mixed Phenotype (n=47)
Prognostic indices for lung cancer				
PNI	49.76±5.08	50.82±4.26	49.88±5.45	48.82±5.19
NLR	2.40±1.60	2.37±1.78	2.35±1.69	2.48±1.38
PLR	131.82±71.45	141.22±100.64	120.22±55.93	136.66±56.67
ALI	50.10±23.42	57.20±26.25	47.25±18.59	47.48±24.93
mGPS	0.10±0.35	0.03±0.17	0.06±0.24	0.19±0.50
PI	0.11±0.34	0.06±0.23	0.10±0.31	0.17±0.43
Regular treatment for COPD before surgery				
LAMA	39 (29.5%)	11 (30.6%)	14 (28.6%)	14 (29.8%)
LABA	36 (27.3%)	14 (38.9%)	11 (22.4%)	11 (23.4%)
ICS	18 (13.6%)	9 (25.0%)	5 (10.2%)	4 (8.5%)
Comorbidities before surgery				
Hypertension	51 (38.6%)	19 (52.8%)	14 (28.6%)	18 (38.3%)
Diabetes mellitus	20 (15.2%)	7 (19.4%)	5 (10.2%)	8 (17.0%)
Cardiovascular disease	13 (9.8%)	3 (8.3%)	4 (8.2%)	6 (12.8%)
Arrhythmia	6 (4.5%)	2 (5.6%)	2 (4.1%)	2 (4.3%)
Peptic ulcer and/or Gastoroesophageal reflux disease	12 (9.1%)	3 (8.3%)	5 (10.2%)	4 (8.5%)

Notes: Values are given as mean±SD or n (%) unless otherwise noted. **p<0.01, *p<0.05 vs non-emphysema phenotype; ††p<0.01, †p<0.05 vs emphysema phenotype.
Abbreviations: BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; PS, performance status; mMRC, modified British Medical Research Council; LAA, low attenuation area; WA%, percentage of airway wall area; ESM_{CSA}, cross-sectional area of erector spinae muscles; VC, vital capacity; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; DLCO, diffusing capacity for carbon monoxide; DLCO/VA, diffusing capacity for carbon monoxide corrected for alveolar volume; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ALI, Advanced Lung Cancer Inflammation Index; mGPS, modified Glasgow Prognostic Score; PI, prognostic index; LAMA, long-acting muscarinic antagonist; LABA, long-acting β_2 agonist; ICS, inhaled corticosteroid.

current smokers was significantly higher in the emphysema phenotype than in the non-emphysema phenotype. The performance status and mMRC dyspnea scale were significantly higher in the mixed phenotype than in the other phenotypes. In pulmonary function, vital capacity (VC) and forced vital capacity (FVC) were significantly higher in the emphysema phenotype than in the mixed phenotype. RV was significantly higher in the mixed phenotype than in the other phenotypes. The parameters of diffusing capacity were significantly higher in the non-emphysema phenotype than in the other phenotypes. There were no significant differences in prognostic indices for lung cancer, regular treatment for COPD before surgery and comorbidities before surgery among the three phenotypes.

Table 2 provides the details of lung cancer including histological diagnoses, pathological stage, type of resection, post-operative complications, and postoperative chemotherapy in these patients. Regarding the histological diagnosis of lung cancer, the proportion of squamous cell carcinoma was significantly higher in the mixed phenotype, and the proportion of adenocarcinoma was significantly higher in the non-emphysema phenotype than in the other phenotypes. There were no significant differences in the proportion of postoperative complications and postoperative chemotherapy among the three phenotypes.

Table 3 shows the number of deaths at the end of the study and the causes of deaths in these patients. There were no significant differences in the causes of deaths among the three phenotypes.

Table 2 Histological Diagnosis, Pathological Stage, Type of Resection, Postoperative Complications Following Pulmonary Resection, and Postoperative Chemotherapy for the Three Phenotypes in Surgically Resected Patients with COPD and Concomitant Lung Cancer

	All Subjects (n=132)	Non-Emphysema Phenotype (n=36)	Emphysema Phenotype (n=49)	Mixed Phenotype (n=47)
Histological diagnosis				
Small cell carcinoma	3 (2.3%)	1 (2.8%)	0 (0.0%)	2 (4.3%)
Squamous cell carcinoma	52 (39.4%)	4 (11.1%)	19 (38.8%) *	29 (61.7%) **†
Adenocarcinoma	69 (52.3%)	28 (77.8%)	26 (53.1%) *	15 (31.9%) **
Large cell carcinoma	6 (4.5%)	2 (5.6%)	3 (6.1%)	1 (2.1%)
Other non-small cell carcinoma	2 (1.5%)	1 (2.8%)	1 (2.0%)	0 (0.0%)
Pathological stage (7th edition)				
Stage I A, B	98 (74.2%)	30 (83.3%)	32 (71.4%)	36 (76.6%)
Stage II A, B	24 (18.2%)	3 (8.3%)	10 (20.4%)	11 (23.4%)
Stage III A, B	9 (6.8%)	2 (5.6%)	7 (14.3%)	0 (0.0%)†
Stage IV	1 (7.6%)	1 (2.8%)	0 (0.0%)	0 (0.0%)
Advanced stage (IIIB, IV)	1 (7.6%)	1 (2.8%)	0 (0.0%)	0 (0.0%)
Type of resection				
Segmentectomy	16 (12.1%)	3 (8.3%)	7 (14.3%)	6 (12.8%)
Lobectomy	114 (86.4%)	33 (91.7%)	41 (83.7%)	40 (85.1%)
Pneumonectomy	2 (1.5%)	0 (0.0%)	1 (2.0%)	1 (2.1%)
Postoperative complications following pulmonary resection				
Acute exacerbation of COPD	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bacterial pneumonia	8 (6.1%)	3 (8.3%)	3 (6.1%)	2 (4.3%)
Pyothorax	8 (6.1%)	3 (8.3%)	1 (2.0%)	4 (8.5%)
Hypoxemia (respiratory failure)	12 (9.1%)	1 (2.8%)	6 (12.2%)	5 (10.6%)
Prolonged air leak	12 (9.1%)	6 (16.7%)	3 (6.1%)	3 (6.4%)
Paroxysmal atrial fibrillation	12 (9.1%)	2 (5.6%)	7 (14.3%)	3 (6.4%)
Others	5 (3.8%)	1 (2.8%)	3 (6.1%)	1 (2.1%)
Surgery-related death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Postoperative chemotherapy and radiation therapy				
Adjuvant chemotherapy	32 (24.2%)	6 (16.7%)	16 (32.7%)	10 (21.3%)
Postoperative recurrence of lung cancer	43 (32.6%)	8 (22.2%)	16 (32.7%)	19 (40.4%)
Chemotherapy after developing recurrence	30 (22.7%)	5 (13.9%)	10 (20.4%)	15 (31.9%)
Chemotherapy-related death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Radiation therapy after developing recurrence	8 (6.1%)	2 (5.6%)	2 (4.1%)	4 (8.5%)

Notes: Values are given as n (%). **p<0.01, *p<0.05 vs non-emphysema phenotype; †p<0.05 vs emphysema phenotype.

Table 3 Causes of Deaths in Surgically Resected Patients with COPD and Concomitant Lung Cancer

	All Subjects (n=132)	Non-Emphysema Phenotype (n=36)	Emphysema Phenotype (n=49)	Mixed Phenotype (n=47)
Number of deaths	68	10	21	37
Lung cancer	34 (50.0%)	6 (60.0%)	12 (57.1%)	16 (44.4%)
Pneumonia	13 (19.1%)	2 (20.0%)	1 (4.8%)	10 (27.8%)
Acute exacerbation of COPD	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
Chronic respiratory failure	3 (4.4%)	1 (10.0%)	0 (0.0%)	2 (5.6%)
Other causes	17 (25.0%)	1 (10.0%)	8 (38.1%)	8 (22.2%)

Note: Values are given as n (%).

Table 4 shows the univariate and multivariate Cox proportional hazard regression analysis of the risk of death. The univariate Cox proportional hazard regression analysis showed that a higher mMRC dyspnea scale and higher LAA score were associated with the risk of death. The multivariate analysis showed that a higher age and higher LAA were independently associated with the risk of death.

Figure 1 shows the Kaplan-Meier curve of the overall survival among the non-emphysema phenotype (n=36, median survival time [MST]: 14.48 years), emphysema phenotype (n=49, MST: 10.38 years), and mixed phenotype (n=47, MST: 5.15 years). In the Kaplan-Meier analysis, the Log rank test showed significant differences in survival between the non-emphysema and mixed phenotypes (p=0.0001), and between the emphysema and mixed phenotypes (p=0.0197). A difference in survival was observed between the non-emphysema and emphysema phenotype (p=0.0661); however, it was not statistically significant.

Discussion

This is the first report to focus on the details of the association between chest CT findings and prognosis in surgically resected patients with COPD and concomitant lung cancer. The mixed phenotype was associated with poorer performance status, greater extent of dyspnea, greater impairment of pulmonary function, higher proportion of squamous cell carcinoma, and shorter survival. The extent of emphysema presented as the LAA score was an independent determinant that predicted prognosis. On the other hand, there were no significant differences in any prognostic indices for lung

Table 4 Univariate and Multivariate Cox Proportional Hazards Regression Analyses of the Risk of Death in Surgically Resected Patients with COPD and Concomitant Lung Cancer (n=132)

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Age	1.10181	0.98544–1.05187	0.2807	1.03828	1.00073–1.07723	0.0456
BMI	0.94708	0.87700–1.02276	0.1657	0.96791	0.88087–1.06355	0.4975
Smoking index	1.00441	0.99835–1.01051	0.1539	1.00048	0.99326–1.00775	0.8962
GOLD stage	1.10382	0.74794–1.62903	0.6189	0.91566	0.62399–1.34366	0.6525
mMRC dyspnea scale	1.48052	1.03362–2.12063	0.0323	1.31875	0.87771–1.98141	0.1829
LAA score	1.04538	1.01383–1.07792	0.0045	1.04791	1.00668–1.09083	0.0223
ESM_{CSA}	0.99995	0.99963–1.00026	0.7511	1.00024	0.99984–1.00064	0.2341

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified British Medical Research Council; LAA, low attenuation area; ESM_{CSA}, cross-sectional area of erector spinae muscles.

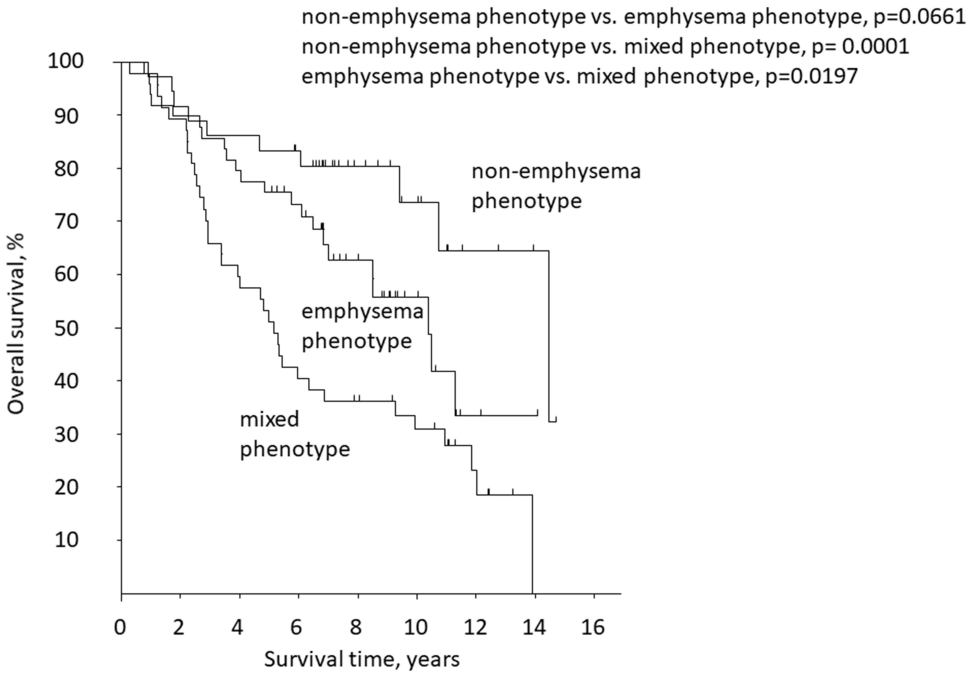

Figure 1 Kaplan-Meier curve of overall survival for non-emphysema phenotype (n=36, MST: 14.48 years), emphysema phenotype (n=49, MST: 10.38 years), and mixed phenotype (n=47, MST: 5.15 years). Differences in survival were assessed using the Log rank test.
Abbreviation: MST, median survival time.

cancer that are indicative of the nutritional and immunological status or the systemic inflammation response among the three phenotypes.

In the present study, we found that the mixed phenotype was associated with a higher proportion of squamous cell carcinoma than the emphysema phenotype without airway wall thickness. Smokers with COPD have a higher risk of developing a specific histological subtype of non-small cell lung cancer termed squamous cell carcinoma.[27] Smith et al reported that the presence of emphysema on chest CT is associated with significantly increased odds of squamous cell carcinoma after adjusting for smoking history.[28] Analysis by grade of emphysema yielded similar results, with an increase in the odds of squamous histology observed in parallel to increasing emphysema severity.[28] In contrast, no report has yet described the association between squamous cell carcinoma and bronchial wall thickness on chest CT in COPD. Little is known about the differences in mechanisms involved in lung cancer development among COPD phenotypes; however, we speculate that the mixed phenotype exhibited worse pulmonary function than the other phenotypes, which may result in the impaired clearance of carcinogenic substances from the airway. We also speculate that airway disease that presented as bronchial wall thickness on chest CT may be preneoplastic lesions of squamous cell lung carcinoma, though the precise timing of alterations during the sequential phases of squamous cell lung carcinoma development in COPD patients is still unknown.[27]

In addition to the LAA score, we used WA% as a parameter of bronchial wall thickness in the present study, though there are various other parameters, such as AWT-Pi10 and airway inner luminal area.[29,30] The reason is because that measurement of the WA% of B10 is relatively easy to apply in clinical practice. Quantitative CT has been increasingly applied to patients with COPD.[29,31,32] However, imaging software programs for quantitative CT sometimes have a problem with availability in clinical practice. Furthermore, the image acquisition and analysis protocols may have differed among various studies that used quantitative CT. This difference was due to the lack of an international consensus concerning the methodology of quantitative CT. In contrast, a visual assessment of the extent of emphysema is based on an established method[24] and can easily be applied to all patients with COPD who underwent chest CT in clinical practice, though it is a semi-quantitative method that cannot fully eliminate inter-observer and intra-observer variation. Therefore, we speculate that our methodology is helpful to understanding the clinical characteristics of surgically resected patients with COPD and concomitant lung cancer because of its simplicity and availability.

In the mixed phenotype, which had both a high LAA score and high WA%, the extent of dyspnea was greater, performance status poorer, and pulmonary function impairment greater than in the other phenotypes, which may result in the poorer prognosis in the present study. These findings suggest that earlier intensive therapeutic intervention for COPD, such as the addition of inhaled bronchodilators and pulmonary rehabilitation, should be applied to this phenotype than the other phenotypes. In addition, limited resection for primary lung cancer may be considered in the mixed phenotype because of their poorer prognosis. Thus, the combination of LAA score and WA% may be one of the useful treatable traits for the management of surgically resected patients with COPD and concomitant lung cancer to determine whether early intensive therapeutic intervention for COPD and limited resection for primary lung cancer should be applied, and also one of determinants to predict all-cause mortality.

In the present study, there were no significant differences in the ESM_{CSA} among the three phenotypes, and there was no significant association between ESM_{CSA} and prognosis. However, previous reports revealed the association between ESM_{CSA} and prognosis in various diseases, including COPD.[12,25,26,33] This may be because all subjects had a performance status of 0 or 1 in the present study; thus, few patients exhibited a decrease in ESM_{CSA} that is indicative of sarcopenia. However, the previous report revealed that accelerated loss of ESM_{CSA} is associated with all-cause mortality in patients with COPD.[13] Thus, further study is needed to investigate whether the decline in ESM_{CSA} following surgery is associated with all-cause mortality in surgically resected patients with COPD and concomitant lung cancer.

The present study has several limitations. First, this was a retrospective single-center study, and the sample size was small. Additional prospective studies should be performed with large study populations that include more patients in order to confirm our results. Second, the assessment of the extent of emphysema on chest CT was performed using a visual scoring method,[6,7,22,23] rather than a software-based method. However, the reproducibility of the visual scoring system was demonstrated in our previous report.[7] Third, the differences in regular treatment for COPD, such as inhaled bronchodilator and corticosteroid, among patients may affect the results. In addition, the differences in the postoperative treatment of lung cancer, such as chemotherapy and radiation therapy, among patients may affect the results, though there was no significant difference in the recurrence rate among the three phenotypes.

Conclusion

The cross-sectional preoperative LAA score can predict the prognosis in surgically resected patients with COPD and concomitant lung cancer. The COPD phenotype with both emphysema and bronchial wall thickness on chest CT was associated with poorer performance status, greater extent of dyspnea, greater impairment of pulmonary function, and worse prognosis in these patients.

Disclosure

The authors report no conflicts of interest in this work.

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