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Impact of coexistent preserved ratio impaired spirometry on the survival of patients with lung cancer: Analysis of data from the Korean Association for Lung Cancer Registry

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Abstract

Background: Preserved ratio impaired spirometry (PRISm) is a common spirometric pattern that is associated with respiratory symptoms and higher mortality rates. However, the relationship between lung cancer and PRISm remains unclear. This study investigated the clinical characteristics of lung cancer patients with PRISm and the potential role of PRISm as a prognostic factor.

Methods: We retrospectively reviewed data collected from 2014 to 2015 in the Korean Association for Lung Cancer Registry. We classified all patients into three subgroups according to lung function as follows: normal lung function; PRISm (forced expiratory volume in 1 s [FEV_1] < 80% predicted and FEV_1/forced vital capacity [FVC] ≥ 0.7); and chronic obstructive pulmonary disease (COPD; FEV1/FVC < 0.7). In non–small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), the overall survival period was compared among the three subgroups. The prognostic factors were investigated using Cox regression analysis.

Results: Of the 3763 patients, 38.6%, 40.1%, and 21.3% had normal lung function, COPD, and PRISm, respectively. Patients with PRISm had poorer overall survival than those with COPD or normal lung function in NSCLC and SCLC (Mantel–Cox log-rank test, $p < 0.05$). In the risk-adjusted analysis, overall survival was independently associated with COPD (hazard ratio [HR] 1.209, $p = 0.027$) and PRISm (HR 1.628, $p < 0.001$) in NSCLC, but was only associated with PRISm (HR 1.629, $p = 0.004$) in SCLC.

Conclusions: PRISm is a significant pattern of lung function in patients with lung cancer. At the time of lung cancer diagnosis, pre-existing PRISm should be considered a predictive factor of poor prognosis.

KEYWORDS
chronic obstructive pulmonary disease, lung cancer, mortality, preserved ratio impaired spirometry, prognosis

INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide, and accounted for approximately 1.8 million deaths and 2.2 million new cases in 2020.[1] According to a US report, despite recent technological advances in cancer treatment, only 24% of patients diagnosed with lung cancer survive for 5 years or more.[2] Therefore, predicting the prognosis of patients with lung cancer is important for the selection of the appropriate treatment and clinical follow-up. A previous study showed that several favorable predictors for survival in lung cancer patients include early-stage disease at diagnosis, good performance status, no significant weight loss, and female sex.[3] Several studies have shown that

pulmonary dysfunction, such as chronic obstructive pulmonary disease (COPD), influences the prognosis of patients with lung cancer.[4–9]

The preserved ratio impaired spirometry (PRISm) is a common pattern of pulmonary function that is associated with respiratory symptoms and mortality. PRISm is calculated as the ratio of the forced expiratory volume in 1 s (FEV_1) < 80% of predicted and FEV_1 to a forced vital capacity (FVC) $\geq$ 0.7.[10–13] Several clinical trials have excluded patients with PRISm, compared to COPD patients, and they were not considered a clinical group of interest. Among lung cancer patients, the clinical characteristics of PRISm patients and the role of PRISm as a prognostic factor have not been sufficiently studied. Similar to COPD patients, PRISm patients are characterized by a decrease in FEV_1, which was previously used as an index of the degree of airflow limitation in COPD patients and was also associated with prognosis.[14,15] A decrease in FEV_1 has been reported to be associated with prognosis in lung cancer patients, although no study has been conducted on PRISm patients.[16,17]

The objective of this study was to investigate the clinical characteristics of lung cancer patients with a spirometric PRISm pattern and to determine the role of PRISm as a prognostic factor. Specifically, it aimed to examine the effect of PRISm on the overall survival of lung cancer patients.

METHODS

Date source and study population

The Korean Association for Lung Cancer Registry (KALC-R) project was implemented to accurately identify the pattern of lung cancer incidence in South Korea; to compile basic research data for future lung cancer research; and establish a systematic database of statistical data on the treatment, death, and survival of lung cancer patients.[18,19] The KALC-R aimed to collect staging information on 10% of the total lung cancer incidence, and 10% of the targets were extracted from 13 nationally designated cancer centers and 39 large hospitals by using a systematic extraction method. In February 2020, the Korean Central Cancer Registry (KCCR) had assimilated data on 2621 and 2660 cases of lung cancer occurrence in 2014 and 2015, respectively. We used the nationwide data collected from 2014 to 2015 in the KALC-R. Detailed information on the planning and progress of KALC-R are available at https://kccrsurvey.cancer.go.kr. Of the 5281 patients registered in the KALC-R, we excluded 1518 patients without data on lung function tests (FEV_1 and FVC), and retrospectively enrolled 3763 lung cancer patients in this study.

Based on the results of lung function tests, participants were classified into three groups:[10,20] the PRISm group included patients with an FEV_1 < 80% of the predicted value and an FEV_1/FVC $\geq$0.7; the COPD group included patients with an FEV_1/FVC < 0.7; and the normal lung function group included patients with an FEV_1 $\geq$ 80% of the

predicted value and an FEV_1/FVC $\geq$0.7. The Institutional Review Board of Gyeongsang National University Changwon Hospital approved this study (GNUCH-2021-01-025). The requirement for informed consent was waived because of the retrospective nature of the study.

Variables

Clinical and demographic data, including age, sex, body mass index (BMI), smoking history, pathological type, Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS), clinical stage, results of molecular tests (e.g., epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma receptor tyrosine kinase [ALK] rearrangement), and survival status, were collected. The participants were categorized into four age-stratified subgroups ($\leq$49, 50–59, 60–69, and $\geq$ 70 years) and assigned to four subgroups according to the Asia-Pacific BMI classification (underweight: <18.5; normal: 18.5–22.9; overweight: 23–24.9; obese I: 25.0–29.9; and obese II: $\geq$30 kg/m^2).[21] Ever-smokers were defined as individuals who had a history of smoking prior to the diagnosis of lung cancer. In these patients, smoking was quantified by calculating the pack-years. The normal predicted values of FVC and FEV_1 were calculated using the method described by Choi et al.[22] The clinical stage was categorized into four groups – I, II, III, and IV – based on the criteria defined in the seventh edition of the TNM classification of lung cancer.[23,24] The clinical stage of small cell lung cancer (SCLC) is divided into limited disease and extensive disease.

Statistical analysis

Continuous variables were presented as medians and interquartile ranges (IQRs) and were compared using the Kruskal–Wallis test. Categorical variables, expressed as the numbers and percentages of participants, were compared using the chi-square test. Risk factors for overall survival were analyzed using Cox proportional hazards regression model. Variables with a p-value < 0.20 in the univariate analysis were included in the multivariate analysis. In this risk-adjusted analysis, backward stepwise methods were applied to determine the independent factors that were associated with survival. The survival rate was estimated by using the Kaplan–Meier method and compared using the log-rank (Mantel–Cox) test. Statistical significance was set at p < 0.05. All statistical analyses were performed using SPSS version 25.0 (IBM Corporation).

RESULTS

Characteristics of participants

The baseline characteristics of the enrolled patients are shown in Table 1. Of the 3763 patients, 2690 (71.5%) were male, and the median age of the cohort was 70.0 (IQRs, 61–76) years.

TABLE 1 Baseline characteristics of participants

Variables	Normal ($n = 1451$)	COPD ($n = 1510$)	PRISm ($n = 802$)	Total ($n = 3763$)
Age (years)	65.0 (57.0–73.0)	72.0 (65.0–77.0)	67.0 (58.0–73.0)	70.0 (61.0–76.0)
≤49	129 (8.9)	19 (1.3)	62 (7.7)	210 (55.8)
50–59	350 (24.1)	143 (9.5)	168 (20.9)	661 (17.6)
60–69	440 (30.3)	434 (28.7)	261 (32.5)	1135 (30.2)
≥70	532 (36.7)	914 (60.5)	311 (38.8)	1757 (46.7)
Sex				
Male	804 (55.4)	1329 (88.0)	557 (69.5)	2690 (71.5)
Female	647 (44.6)	181 (12.0)	245 (30.5)	1073 (28.5)
BMI (kg/m^2)	23.4 (21.4–25.6)	22.7 (20.6–24.7)	22.9 (20.4–25.5)	22.9 (20.7–25.1)
<18.5	68 (4.7)	136 (9.3)	77 (9.6)	281 (7.6)
18.5–22.9	564 (38.9)	649 (44.5)	331 (41.3)	1544 (41.6)
23–24.9	383 (26.4)	346 (23.7)	151 (18.9)	880 (23.7)
25–29.9	385 (26.6)	302 (20.7)	211 (26.3)	898 (24.2)
≥30	50 (3.4)	26 (1.8)	31 (3.9)	107 (2.9)
Smoking habit				
Never-smoker	741 (51.2)	231 (15.4)	285 (35.8)	1257 (33.6)
Current smoker	339 (23.4)	736 (49.1)	295 (37.1)	1370 (36.6)
Ex-smoker	367 (25.4)	531 (35.4)	215 (27.0)	1113 (29.8)
Pack-years	30.0 (20.0–44.0)	40.0 (30.0–50.0)	35.0 (20.0–50.0)	40.0 (25.0–50.0)
ECOG PS				
0	713 (61.1)	417 (37.5)	236 (37.1)	1366 (46.9)
1	389 (33.4)	551 (49.5)	296 (46.5)	1236 (42.4)
2	40 (3.4)	103 (9.3)	69 (10.8)	212 (7.3)
3	16 (1.4)	29 (2.6)	25 (3.9)	70 (2.4)
4	8 (0.7)	13 (1.2)	10 (1.6)	31 (1.1)
Lung function				
FVC (L)	3.25 (2.73–3.92)	3.15 (2.52–3.68)	2.44 (1.98–2.97)	3.05 (2.44–3.65)
FVC (% of predicted)	89.9 (82.4–98.2)	79.7 (67.4–90.5)	64.5 (55.8–72.6)	81.2 (68.3–92.2)
FEV$_1$ (L)	2.55 (2.19–3.02)	1.82 (1.39–2.23)	1.88 (1.55–2.26)	2.12 (1.66–2.59)
FEV$_1$ (% of predicted)	94.0 (87.0–103.1)	66.4 (53.4–78.6)	68.8 (60.4–75.0)	78.8 (63.8–91.6)
FEV$_1$/FVC	0.78 (0.74–0.82)	0.61 (0.53–0.66)	0.76 (0.73–0.81)	0.73 (0.64–0.79)
DL$_{CO}$ (% of predicted)	91.0 (0.78–105.0)	75.0 (59.0–89.0)	71.0 (59.0–83.0)	81.0 (65.0–96.0)
Pathology				
Squamous cell carcinoma	238 (16.4)	581 (38.5)	190 (23.7)	1009 (29.3)
Adenocarcinoma	1025 (70.6)	515 (34.1)	407 (50.7)	1947 (56.5)
Large cell carcinoma	11 (0.8)	17 (1.1)	9 (1.1)	37 (1.1)
Small cell lung cancer	85 (5.9)	243 (16.1)	126 (15.7)	454 (13.2)
EGFR mutation	371/935 (39.7)	145/723 (20.1)	154/471 (32.7)	670/2129 (31.5)
ALK IHC or FISH	59/843 (7.0)	28/542 (5.2)	34/341 (10.0)	121/1726 (7.0)
Clinical stage in NSCLC[a]				
I	670 (51.1)	332 (27.5)	122 (18.8)	1124 (35.5)
II	116 (8.8)	137 (11.4)	37 (5.7)	290 (9.2)
III	194 (14.8)	307 (25.4)	118 (18.2)	619 (19.6)
IV	331 (25.2)	431 (35.7)	371 (57.3)	1133 (35.8)
Clinical stage in SCLC[a]				
Limited disease	38 (44.7)	119 (49.0)	41 (35.2)	198 (44.8)
Extensive disease	42 (49.4)	118 (48.6)	84 (66.7)	244 (55.2)

Abbreviations: ALK, anaplastic lymphoma receptor tyrosine kinase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DL$_{CO}$, diffusing capacity for carbon monoxide; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; FEV$_1$, forced expiratory volume in 1 s; FISH, fluorescence in situ hybridization; FVC, forced vital capacity; IHC, immunohistochemistry; NSCLC, non–small cell lung carcinoma; PRISm, preserved ratio impaired spirometry; SCLC, small cell lung carcinoma.

Note: Data are presented as median (interquartile ranges), unless otherwise indicated.

[a]Patients with available data of clinical staging of lung cancer.

The median BMI was 22.9 (IQRs, 20.7–25.1) kg/m^2, and 41.6% of patients were a normal weight. A history of smoking was observed in 66.4% of patients, with a median of 40.0 pack-years. A total of 89.3% of the patients had a good performance status (ECOG 0 or 1). The lung-function characteristics of the participants were as follows: the median FVC, FEV$_1$, and FEV$_1$/FVC values were 81.2 (IQRs, 68.3%–92.2%) of the predicted value, 78.8 (IQRs, 63.8%–91.6%) of the predicted value, and 0.73 (IQRs, 0.64–0.79), respectively. Pathologically, patients were diagnosed with squamous cell carcinoma (29.3%), adenocarcinoma (56.5%), and SCLC (13.2%). Among the patients with non–small cell lung cancer (NSCLC), 35.5%, 9.2%, 19.6%, and 35.8% had stage I, II, III, and IV NSCLC, respectively. In patients with SCLC, 44.8% had a limited disease, while 55.2% had an extensive disease.

Comparison of three groups according to lung function

According to the lung function test, 1510 (40.1%) and 802 (21.3%) patients belonged to the COPD and PRISm groups, respectively. The remaining 1451 (38.6%) patients had normal lung function. These three groups had different distributions of age, sex, and BMI ($p < 0.001$). Overall, compared with patients with PRISm (64.2%) and normal lung function (48.8%), 84.6% of COPD patients were ever-smokers, with a smoking history of median 40.0 (IQRs, 30.0–50.0) pack-years ($p < 0.001$). Patients with PRISm had a worse performance status than those with COPD or normal lung function ($p < 0.001$). In the pulmonary function tests, the FEV$_1$ was lower in PRISm or COPD patients than in patients with normal lung function ($p < 0.001$), but the FVC and diffusion capacity were lower in the PRISm group than in the COPD group (FVC, $p < 0.001$; diffusion capacity, $p = 0.003$). The most common pathological type was squamous cell carcinoma in the COPD group whereas adenocarcinoma was the most common subtype in the PRISm or normal lung function group. The COPD group had the least number of patients with an EGFR mutation (20.1%) or ALK rearrangements (5.2%), whereas patients with PRISm showed EGFR mutations (32.7%) or ALK rearrangements (10.0%). Among NSCLC patients, more than half of the patients with normal lung function were classified as having early stage lung cancer (stage I), whereas 57.3% of participants in the PRISm group had stage IV lung cancer. Among patients with SCLC, 66.7% of the patients in the PRISm group had an extensive disease.

Overall survival rates among the three groups according to lung function

The estimated median overall survival time of patients with NSCLC and SCLC was 31.0 ± 1.6 and 10.0 ± 0.5 months, respectively. Figure 1 presents comparisons of the overall survival rate in the NSCLC and SCLC groups according to the three groups that were stratified by the lung function. In NSCLC, the three groups showed significant differences in the overall survival duration: Mantel–Cox log-rank test, overall $p < 0.001$; normal lung function group vs. COPD group, $p < 0.001$; normal lung function group vs. PRISm group, $p < 0.001$; PRISm group vs. COPD group, $p < 0.001$. Patients with PRISm had the most unfavorable clinical outcomes, with an estimated median overall survival of 14.0 ± 1.0 months. However, patients with normal lung function or COPD had an estimated median survival of 59.0 ± 1.3 or 19.0 ± 1.1 months, respectively. Furthermore, the overall survival duration differed among the three groups according to lung function in SCLC patients (Mantel–Cox log-rank test, overall $p < 0.001$; normal lung
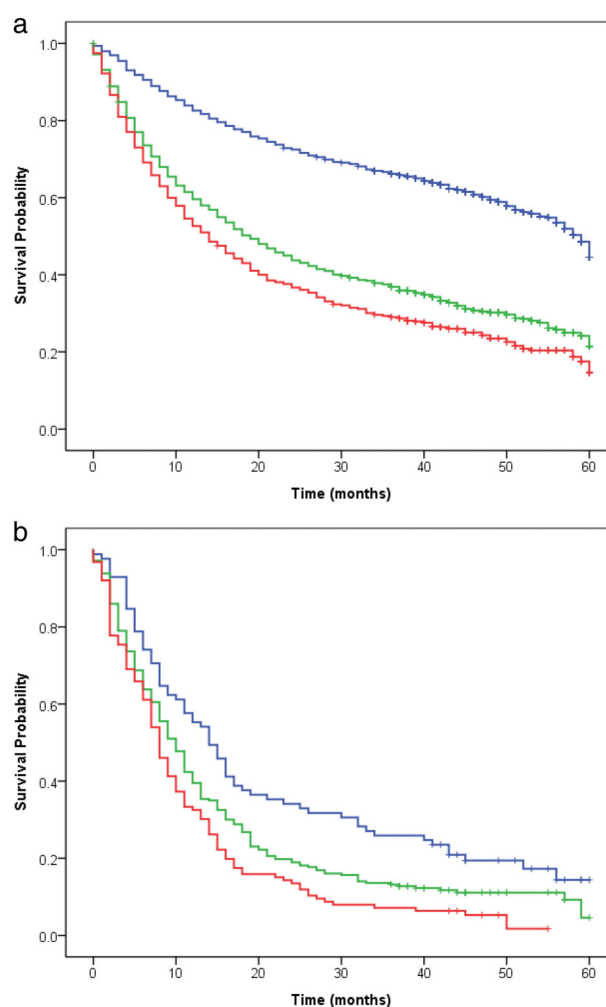

FIGURE 1 Overall survival rate in patients with lung cancer. (a) Non-small cell lung carcinoma; (b) small cell lung carcinoma. In the non-small cell lung carcinoma group, patients with PRISm had poorer overall survival than those with COPD ($p < 0.001$) or normal lung function ($p < 0.001$). In the small cell lung carcinoma group, patients with PRISm had poorer overall survival than those with COPD ($p = 0.018$) or normal lung function ($p < 0.001$). Note: Blue line: normal lung function. Green line: chronic obstructive pulmonary disease (COPD). Red line: preserved ratio impaired spirometry (PRISm)

TABLE 2 Prognostic factors in patients with non–small cell lung carcinoma

Variables	Univariate analysis		Multivariate analysis	
	Exp. (95% CI)	p-value	Exp. (95% CI)	p-value
Age (years)				
≤49	1.000		1.000	
50–59	1.001 (0.803–1.208)	0.989	1.324 (0.987–1.777)	0.061
60–69	1.271 (1.067–1.514)	0.007**	1.675 (1.259–2.228)	<0.001***
≥70	2.069 (1.750–2.446)	<0.001***	2.086 (1.576–2.759)	<0.001***
Sex				
Male	1.000		1.000	
Female	0.569 (0.523–0.619)	<0.001***	0.718 (0.614–0.839)	<0.001***
BMI (kg/m^2)				
<18.5	1.711 (1.511–1.938)	<0.001***	1.335 (1.054–1.692)	0.017*
18.5–22.9	1.000		1.000	
23–24.9	0.701 (0.635–0.774)	<0.001***	0.908 (0.766–1.077)	0.267
25–29.9	0.621 (0.561–0.688)	<0.001***	0.731 (0.613–0.870)	<0.001***
≥30	0.648 (0.505–0.832)	0.001**	1.022 (0.692–1.509)	0.914
Smoking habit				
Never-smoker	1.000			
Current smoker	1.664 (1.525–1.814)	<0.001***		
Ex-smoker	1.394 (1.271–1.530)	<0.001***		
ECOG PS				
0	1.000		1.000	
1	2.366 (2.144–2.612)	<0.001***	1.364 (1.175–1.585)	<0.001***
2	4.040 (3.478–4.693)	<0.001***	1.485 (1.163–1.895)	0.002**
3	6.017 (4.912–7.370)	<0.001***	2.103 (1.432–3.088)	<0.001***
4	7.250 (5.535–9.497)	<0.001***	4.895 (2.583–9.277)	<0.001***
Pathology				
Adenocarcinoma	0.515 (0.479–0.554)	<0.001***	0.819 (0.698–0.960)	0.014*
EGFR	0.597 (0.538–0.663	<0.001***	0.696 (0.595–0.813)	<0.001***
ALK IHC or FISH	0.947 (0.768–1.167)	0.608		
Clinical stage				
I	1.000		1.000	
II	2.321 (1.921–2.805)	<0.001***	1.847 (1.332–2.560)	<0.001***
III	5.104 (4.449–5.855)	<0.001***	4.096 (3.213–5.222)	<0.001***
IV	8.593 (7.599–9.717)	<0.001***	7.240 (5.822–9.003)	<0.001***
Lung function group				
Normal	1.000		1.000	
COPD	2.319 (2.086–2.578)	<0.001***	1.209 (1.022–1.431)	0.027*
PRISm	2.829 (2.509–3.190)	<0.001***	1.628 (1.373–1.930)	<0.001***

Abbreviations: ALK, anaplastic lymphoma receptor tyrosine kinase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; PRISm, preserved ratio impaired spirometry.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

function group vs. COPD group, $p = 0.007$; normal lung function group vs. PRISm group, $p < 0.001$; PRISm group vs. COPD group, $p = 0.018$).The patients with PRISm had a shorter median survival duration (8.0 ± 0.7 months) than patients with COPD (10.0 ± 0.7 months) or normal lung function (14.0 ± 1.5 months).

Prognostic role of PRISm

To examine the role of PRISm as a predictor of prognosis in lung cancer, a survival analysis was conducted. The prognostic factors for overall survival in NSCLC patients are shown in Table 2, and old age, male sex, being underweight,

T A B L E 3 Prognostic factors in patients with small cell lung carcinoma

	Univariate analysis		Multivariate analysis	
Variables	Exp. (95% CI)	p-value	Exp. (95% CI)	p-value
Age (years)				
≤49	1.000		1.000	
50–59	1.195 (0.703–2.032)	0.511	1.726 (0.686–4.343)	0.246
60–69	1.344 (0.806–2.243)	0.257	1.911 (0.766–4.766)	0.165
≥70	2.114 (1.280–3.491)	0.003**	3.200 (1.297–7.896)	0.012*
Sex				
Male	1.000			
Female	0.903 (0.724–1.127)	0.368		
BMI (kg/m²)				
<18.5	1.715 (1.287–2.286)	<0.001***	1.443 (0.895–2.325)	0.132
18.5–22.9	1.000		1.000	
23–24.9	0.858 (0.693–1.602)	0.159	0.883 (0.657–2.325)	0.411
25–29.9	0.694 (0.563–0.854)	0.001**	0.719 (0.546–0.946)	0.019*
≥30	0.842 (0.527–1.344)	0.471	0.491 (0.239–1.009)	0.053
Smoking habit				
Never-smoker	1.000			
Current smoker	0.670 (0.537–0.836)	<0.001***		
Ex-smoker	0.675 (0.531–0.856)	0.001**		
ECOG PS				
0	1.000		1.000	
1	1.020 (0.832–1.250)	0.852	0.928 (0.723–1.190)	0.555
2	1.865 (1.361–2.556)	<0.001***	1.925 (1.292–2.868)	0.001**
3	2.683 (1.692–4.257)	<0.001***	1.496 (0.678–3.298)	0.318
4	3.419 (2.033–5.748)	<0.001***	2.709 (1.067–6.879)	0.036*
Clinical stage				
Limited disease	1.000		1.000	
Extensive disease	2.145 (1.805–2.548)	<0.001***	2.142 (1.688–2.717)	<0.001***
Lung function group				
Normal	1.000		1.000	
COPD	1.439 (1.097–1.886)	0.008**	1.240 (0.912–1.685)	0.169
PRISm	1.864 (1.385–2.510)	<0.001***	1.629 (1.166–2.275)	0.004**

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PRISm, preserved ratio impaired spirometry.

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

ever-smokers, poor performance status (ECOG 1–4), advanced clinical stage (II–IV), COPD, and PRISm were associated with adverse prognosis in the univariate analysis. This result showed that female sex, being overweight, obesity, adenocarcinoma, and *EGFR* mutations were favorable predictors of prognosis. On multivariate analysis, age ≥ 60 years, male sex, underweight, poor performance status (ECOG 1–4), advanced clinical stage (II–IV), COPD, and PRISm remained significant predictors of unfavorable overall survival in NSCLC patients. In contrast, female sex, obese I, pathological adenocarcinoma, and *EGFR* mutation were independent predictive factors for prolonged survival.

The prognostic factors of overall survival in patients with SCLC are shown in Table 3. In SCLC, age ≥ 70 years, underweight, poor performance status (ECOG 2–4), extensive disease, COPD, or PRISm had poor overall survival rates in the univariate analysis. Furthermore, the results showed that SCLC patients who were in the obese I group or had an ever-smoking history had a favorable prognosis. Subsequently, multivariate analysis showed that age ≥ 70 years, poor performance status (ECOG 2 or 4), extensive disease, and PRISm were associated with a shorter overall survival rate. In contrast, obesity had a beneficial effect on survival in SCLC patients.

DISCUSSION

Pulmonary dysfunction can adversely affect lung cancer prognosis. In particular, lung cancer patients with PRISm showed a shorter overall survival time than those with COPD or normal lung function in this Korean lung cancer cohort. COPD was a significant independent prognostic factor only in SCLC; however, PRISm was identified as an important prognostic factor not only in SCLC but also in NSCLC. To the best of our knowledge, this is the first report of the prognostic role of PRISm in lung cancer.

PRISm is a distinct disease category that shows different lung function patterns in COPD. This study showed that the PRISm group had a lower FVC and diffusing capacity for carbon monoxide (DL_{CO}) than the COPD group. PRISm is characterized by a decrease in the FVC and has been previously categorized as a restrictive lung disease. Thus, the clinical features of PRISm patients can be identified through available evidence on restrictive lung diseases. In previous studies, PRISm was related to the metabolic syndrome and systemic inflammation.[25–27] In addition, patients with PRISm have shown a high cardiovascular burden, early mortality, and impaired health-related quality of life.[13,28] In this study, compared to the COPD group, the PRISm group had no difference in the mean BMI but comprised younger participants, more women, and more non-smokers. However, it consisted of a higher proportion of male participants and ever-smokers with poorer performance status than those with normal lung function. This is similar to the attributes of PRISm patients that were reported in previous studies in the general population, but with differences in BMI and age distribution. They were likely to be older, male, ever-smokers, and more obese than the participants in the control group.[28] This suggests that lung cancer could affect the clinical characteristics of patients with PRISm.

Previous studies have reported that a decrease in FEV_1 adversely affects the prognosis of lung cancer.[16,17,29,30] The decline in FEV_1 is a common feature that can be seen in both COPD and PRISm. In this study, there was no significant difference in the volume or predicted value of FEV_1 between the PRISm and COPD groups. However, the FEV_1 level did not play a prognostic role in risk-adjusted mortality analysis in lung cancer patients with PRISm (data not shown). On the other hand, PRISm patients had other factors of poor prognosis in NSCLC, including higher age, male sex, poor performance status, and advanced clinical stage. Older age and poor performance are independent risk factors for SCLC. These variables have been cited as predictors of survival in several previous studies of lung cancer.[3,31–35] Therefore, we confirmed that these variables are important prognostic factors for lung cancer, even in patients with PRISm.

Many studies have evaluated the association between COPD and the prognosis of lung cancer, but the results have not been consistent. This inconsistence can be attributed to the heterogeneity of the study population.[7,36] The lung cancer stage, pathology, and treatment of patients differ in each study; therefore, the effects of COPD may differ in studies with different populations. A number of studies have previously reported that COPD has a greater impact on early-stage lung cancer than on advanced-stage lung cancer.[5,37,38] In this study, we confirmed that COPD is a significant independent prognostic factor in NSCLC patients, even after adjusting other confounders, such as the stage of lung cancer. This finding is consistent with previously reported findings.[4–7,39] However, we determined that COPD was not an independent prognostic factor in SCLC. Furthermore, previous studies have shown that COPD is not associated with mortality in SCLC.[16,40]

Several limitations of this study should be considered when interpreting these results. First, this study was conducted using systematically extracted data, and did not include all the data on lung cancer patients in South Korea. In addition, this study was conducted only among patients who had data available on the results of pulmonary function tests; thus, a selection bias may exist. In general, patients who do not undergo lung function tests are presumed to have advanced lung cancer that is associated with functional limitations or inability to receive localized treatment, such as surgery. Second, post-bronchodilator pulmonary function tests were not performed in all patients. Third, the registry data did not provide an exact date of death, but only the month when the death occurred; therefore, the overall survival calculation may differ from the actual survival period. Fourth, the cause-and-effect relationship between pulmonary dysfunction and the progression of lung cancer could not be clarified. Lung cancer invades the airway and impairs the lung function, which can be indirectly determined by the presence of main bronchus invasion or obstructive pneumonitis. However, there was no statistically significant difference between the PRISm group and the COPD group ($p > 0.05$). Lastly, the KALC-R does not provide enough information about the underlying respiratory diseases, such as interstitial pneumonia, to determine the cause of PRISm in this study. We believe further research to investigate the relationship between the etiology of PRISm and lung cancer is needed in the future. Despite these limitations, the KALC-R has data from a nationwide survey and is statistically reliable data source of nationally representative data.

In conclusion, patients with PRISm or COPD had a shorter overall survival period than those with normal lung function in both NSCLC and SCLC groups. In particular, patients with PRISm accounted for 21% of all patients with lung cancer in this study. The risk-adjustment analysis showed that PRISm was an independent prognostic factor in SCLC and NSCLC. Therefore, when developing a lung cancer treatment plan, it is necessary to consider the likelihood of a poor prognosis in patients diagnosed with PRISm on lung function tests.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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