

# Impact of COPD on prognosis of lung cancer: from a perspective on disease heterogeneity

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**Background:** COPD is an important comorbidity of lung cancer, but the impact of COPD on the outcomes of lung cancer remains uncertain. Because both COPD and lung cancer are heterogeneous diseases, we evaluated the link between COPD phenotypes and the prognosis of different histological subtypes of lung cancer.

**Methods:** In this retrospective study, subjects with a newly and pathologically confirmed diagnosis of lung cancer were enrolled from patients preparing for lung cancer surgery. All participants underwent pulmonary function test (PFT). The diagnosis of COPD was based on GOLD criteria. Lung cancer subtypes and COPD phenotypes were categorized by WHO classification of lung tumors and computer quantitative analysis of PFT. The HRs were estimated by Cox regression analysis.

**Results:** Among 2,222 lung cancer patients, 32.6% coexisted with COPD. After adjustment for age, sex, body mass index (BMI), smoking status, and therapy method, COPD was significantly associated with the decreased overall survival (OS) of lung cancer (HR 1.28, 95% CI 1.05–1.57). With the increased severity of COPD, the OS of lung cancer was gradually worsened (HR 1.23, 95% CI 1.08–1.39). But surgical treatment and high BMI were independent prognostic protective factors (HR 0.46, 95% CI 0.37–0.56; HR 0.96, 95% CI 0.94–0.99). Moreover, in terms of disease heterogeneity, emphysema-predominant phenotype of COPD was an independent prognostic risk factor for squamous carcinoma (HR 2.53, 95% CI 1.49–4.30). No significant relationship between COPD phenotype and lung cancer prognosis was observed among adenocarcinoma, small cell lung cancer, large cell lung cancer, and other subtype patients.

**Conclusion:** These findings suggest that COPD, especially emphysema-predominant phenotype, is an independent prognostic risk factor for squamous carcinoma only.

**Keywords:** lung cancer, COPD, prognosis, histology, disease heterogeneity

## Introduction

Lung cancer and COPD are both devastating diseases. Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths worldwide,<sup>1</sup> with approximately 10%–20% 5-year survival rate.<sup>2</sup> It has become the fifth cause of deaths globally.<sup>3</sup> In 2015, an estimated 610,200 patients died due to lung cancer in China.<sup>4</sup> COPD is another common pulmonary disease that imposes a significant burden in terms of health care costs, disability, and impaired life quality.<sup>5</sup> In 2010, COPD accounted for about 5.2 million deaths<sup>6</sup> and ranked third among the cause of deaths globally.<sup>3</sup> Both lung cancer and COPD have been the most challenging medical issues faced by China, even entire world.

Lung cancer and COPD are closely related<sup>7</sup> and share many common risk factors, especially cigarette smoking.<sup>8–11</sup> Whereas previous studies have reported an increased

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risk of lung cancer due to COPD by 2- to 6-fold regardless of smoking habits,<sup>12–15</sup> even in nonsmokers.<sup>16</sup> Meanwhile, COPD is considered to be an important comorbidity of lung cancer, and about 40%–70% of lung cancer patients coexist with COPD.<sup>13,17,18</sup> Therefore, several studies have attempted to investigate the relationship between COPD and prognosis of lung cancer. Researchers have pointed out COPD as an important risk factor for respiratory-related complications and postoperative recurrence of non-small cell lung cancer (NSCLC)<sup>19</sup> and found that lung cancer coexisting with COPD led to poor prognosis. But a few other researchers reported contradictory results.<sup>20</sup> The impact of COPD on the prognosis of lung cancer remains uncertain and needs to be further elucidated.

Lung cancer and COPD themselves are heterogeneous diseases with different pathological changes, clinical manifestations, and outcomes. So, we speculated that the heterogeneous nature of the two diseases played an important role in the relationship between COPD and lung cancer prognosis. Generally, lung cancer is categorized according to the histopathology and WHO classification method,<sup>21</sup> while COPD can be divided into two most common phenotypes according to the dominant clinical feature and pathological changes: emphysema-predominant and chronic bronchitis-predominant phenotypes.<sup>22,23</sup>

To confirm the above hypothesis, we conducted this study with a large sample to clarify the impact of COPD on lung cancer prognosis and further explored the relationships between COPD phenotypes and the prognosis of different histological subtypes of lung cancer.

## Materials and methods

### Patients

We performed a retrospective cohort study using the clinical data of Qilu Hospital, Shandong University, Jinan, People's Republic of China. The study was approved by the Institutional Review Board of this hospital and was in accordance with the ethical standards and the Declaration of Helsinki (No 2015091). From October 2004 to December 2015, patients with newly and pathologically confirmed diagnosis of lung cancer who were preparing for lung cancer surgery were enrolled. All participants had undergone pulmonary function test (PFT). Histological subtypes of lung cancer were determined based on preoperative and/or postoperative histopathology reports and were categorized as squamous carcinoma, adenocarcinoma, small cell lung cancer (SCLC), large cell lung cancer (LCLC; including large cell neuroendocrine carcinoma), and other histological types according to 2015

WHO classification of lung tumors.<sup>21</sup> Patients were excluded if they presented with simultaneous or sequential second primary cancers or had a history of asthma, bronchiectasis, tuberculosis, pulmonary fibrosis, or other confounding diseases. Data on age, sex, body mass index (BMI), smoking history, lung cancer histology, chest computed tomography (CT), therapy method, and other medical information were carefully collected for all subjects included in the study. The PFT data of all patients were derived from the MasterLab system (Jaeger, Hoechberg, Germany) of the hospital, including forced vital capacity (FVC), forced expiratory volume in 1 second ( $FEV_1$ ), and raw data points (sampling every 40 mL of volume) of the maximum expiratory flow volume (MEFV) curve.

As a retrospective study, all data were anonymous. We declared that patients' data were confidential and did not compromise the patient's interests. After the approval of the Ethics Committee of Qilu Hospital of Shandong University, informed consent from participants was not required.

### Assessment of COPD

All PFTs were performed and evaluated by experienced respiratory physicians on a computerized spirometer (MasterScreen, Jaeger) according to the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations.<sup>24</sup> The GOLD criteria was used to diagnose and assign severity of COPD: patients with a postbronchodilator  $FEV_1/FVC < 0.70$  were classified as having COPD;  $FEV_1 \geq 0.8$  was defined as mild,  $0.5 \leq FEV_1 < 0.8$  as moderate,  $0.3 \leq FEV_1 < 0.5$  as severe, and  $FEV_1 \leq 0.3$  as extremely severe.<sup>25</sup>

### Identification of COPD phenotypes

Previous studies have demonstrated that a sharp "angle of collapse" (airway collapse [AC]) in the MEFV curve was an effective indicator for emphysema.<sup>26,27</sup> We referred to the Topalovic's method to make a quantitative measurement of AC.<sup>27</sup> According to our previous research,<sup>28</sup> the raw PFT data points of the MEFV curve were reestablished and analyzed by a computer model. The ACs were measured with standard procedures using the computer model based on Matlab software 8.5 (The MathWorks, Natick, MA, USA). AC  $137^\circ$  was chosen as an optimal cutoff point for categorizing COPD phenotypes: emphysema-predominant phenotype ( $AC \leq 137^\circ$ ) and nonemphysema-predominant phenotype ( $AC > 137^\circ$ ). A few COPD patients, whose raw PFT data were not available for AC measurement, were excluded from further analysis related to COPD phenotype.

## Follow-up

All patients were followed up to determine their survival status. These survival data were collected from the hospitals, the Civil Administration Bureau, the Public Security Bureaus, or the description of patient's family members. The primary end point of this study was overall survival (OS). OS was measured from the day of diagnosis to the date of death or date of last follow-up visit.

## Statistical analysis

All statistical analyses were performed using SPSS version 19.0 for windows (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean  $\pm$  SD, and comparison between the groups was done using Student's *t*-test. Categorical variables were presented as percentages, and comparison between the groups was done using the chi-squared test. Survival curves were generated using the Kaplan–Meier method, and the difference between the survival curves in relation to low and high levels of prognostic factors was tested using the log-rank test. Cox regression analysis was used to evaluate the HR as well as 95% confidence intervals. A two-sided *P*-value  $<0.05$  was deemed statistically significant.

## Results

### Patient characteristics

A total of 2,222 patients with newly diagnosed lung cancer were enrolled in this study. The characteristics of patients are provided in Table 1. The age of lung cancer patients was  $60.2 \pm 9.5$  years. Of the total number of patients, 1,670 (75.2%) were male and 1,187 (53.4%) were current smokers or ex-smokers. The histological subtypes identified were as follows: squamous carcinoma (792 [35.6%]), adenocarcinoma (1,120 [50.4%]), SCLC (152 [6.8%]), LCLC (78 [3.5%]), and other histologic types (including adenosquamous, carcinoma carcinoïd tumors, sarcomatoid carcinoma, and pulmonary melanoma; 80 [3.6%]). Moreover, 2,061 (92.8%) lung cancers were at early stage (stage IA–IIB) and 1,821 (80.1%) of all lung cancers had eventually undergone surgery.

The prevalence of COPD in lung cancer patients was 32.6%. Five hundred forty (74.6%) COPD patients were categorized as mild, 155 (21.4%) were moderate, and 29 (4.0%) were severe or extremely severe. Compared with lung cancer patients with non-COPD, those with COPD were older ( $P < 0.001$ ), had a lower BMI ( $P < 0.001$ ), and majority were male ( $P < 0.001$ ) and smokers ( $P < 0.001$ ). The proportion of squamous carcinoma was higher in patients with COPD, while adenocarcinoma was more frequently observed in

patients with non-COPD. Furthermore, 656 (90.6%) COPD patients had undergone computer quantitative measurements of AC. Seventy-five emphysema-predominant phenotype ( $AC = 128.6^\circ \pm 7.0^\circ$ ) and 581 nonemphysema-predominant phenotype ( $AC = 151.1^\circ \pm 7.2^\circ$ ) in COPD patients were identified. Other characteristics of the two phenotypes are shown in Table 2.

## OS analysis

The median follow-up period was 49.9 months, with a follow-up rate exceeding 95% (2,112 of 2,222 lung cancers). The 3-/5-year OS rates of lung cancers were 73.0%/65.2% in COPD patients and were 79.5%/73.3% in non-COPD patients. The Kaplan–Meier survival curves indicated that COPD, COPD severity, and its phenotypes were significantly associated with worse OS of lung cancers ( $P < 0.001$ ). Besides, surgical treatment was also considered as one of the factors that significantly affects the prognosis of lung cancer ( $P < 0.001$ , Figure 1).

The HRs of factors related to lung cancer prognosis are shown in Table 3. In univariate analysis, the presence of COPD was associated with the decreased OS of lung cancer (HR = 1.46, 95% CI 1.20–1.76), and similarly both emphysema-predominant phenotype and nonemphysema-predominant phenotype of COPD significantly decreased the OS (HR = 1.35, 95% CI 1.20–1.53). However, surgical treatment and high BMI were demonstrated as prognostic protective factors (HR 0.44, 95% CI 0.36–0.54; HR 0.95, 95% CI 0.93–0.98). Multivariate Cox regression analysis showed that, after adjustment for age, sex, BMI, smoking status, and therapy method, COPD (especially emphysema-predominant phenotype) was significantly associated with the decreased OS of lung cancers (HR 1.28, 95% CI 1.05–1.57; HR 1.84, 95% CI 1.21–2.80). With the increased severity of COPD, the prognosis of lung cancer was gradually worsened (HR 1.23, 95% CI 1.08–1.39). Conversely, the presence of nonemphysema-predominant phenotype of COPD showed no impact on the prognosis of lung cancer (HR 1.14, 95% CI 0.91–1.43). Furthermore, the same Cox regression model demonstrated that lower age was another prognostic protective factor besides surgical treatment and high BMI.

The HRs for OS according to different grades of COPD severity among lung cancer patients are shown in Table 4. In univariate analysis, the presence of any grades of COPD, especially those categorized as emphysema-predominant phenotype of COPD, was significantly associated with the decreased OS of lung cancer. Nonemphysema-predominant phenotype of moderate COPD also decreased the OS.

**Table 1** Characteristics of lung cancers

Characteristics	Entire cohort (n=2,222)	COPD (n=724)	Non-COPD (n=1,498)	P-value <sup>a</sup>
Age, years (mean ± SD)	60.2±9.5	62.6±8.5	59.1±9.7	<0.001
Sex, n (%)				<0.001
Male	1,670 (75.2)	636 (87.8)	1,034 (69.0)	
Female	552 (24.8)	88 (12.2)	464 (31.0)	
BMI, kg/m <sup>2</sup> (mean ± SD)	24.2±3.5	23.7±3.5	24.5±3.4	<0.001
Smoking status, n (%)				<0.001
Current and ex-smokers	1,187 (53.4)	499 (68.9)	688 (45.9)	
Nonsmokers	1,035 (46.6)	225 (31.1)	810 (54.1)	
Histology, n (%)				
Squamous carcinoma	792 (35.6)	341 (47.1)	451 (30.1)	<0.001
Adenocarcinoma	1,120 (50.4)	263 (36.3)	857 (57.2)	<0.001
SCLC	152 (6.8)	65 (9.0)	87 (5.8)	0.004
LCLC	78 (3.5)	31 (4.3)	47 (3.1)	0.107
Other subtypes <sup>b</sup>	80 (3.6)	24 (3.3)	56 (3.7)	0.356
Treatment, n (%)				
Surgery	1,821 (82.0)	549 (75.8)	1,272 (84.9)	<0.001
Nonsurgery	401 (18.0)	175 (24.2)	226 (15.1)	
Chemotherapy and/or radiotherapy	327 (14.7)	139 (19.2)	188 (12.6)	<0.001
Palliative therapy	74 (3.3)	36 (5.0)	38 (2.5)	<0.001
Clinical stage, n (%)				
I	1,598 (71.9)	531 (73.3)	1,067 (71.2)	0.314
II	463 (20.9)	152 (21.0)	311 (20.8)	0.911
III–IV	161 (7.2)	41 (5.7)	120 (8.0)	0.045
FVC, L (mean ± SD)	3.3±0.8	3.2±0.7	3.4±0.8	<0.001
FVC% predicted, % (mean ± SD)	101.59±16.8	96.1±18.0	104.6±15.5	<0.001
FEV <sub>1</sub> , L (mean ± SD)	2.5±0.7	2.0±0.5	2.7±0.6	<0.001
FEV <sub>1</sub> predicted, % (mean ± SD)	95.0±20.3	76.5±16.9	103.9±15.2	<0.001
FEV <sub>1</sub> /FVC, % (mean ± SD)	73.5±9.8	61.9±6.4	79.2±5.1	<0.001
COPD				
No	1,498 (67.4)	/	1,498 (100)	
Yes	724 (32.6)	724 (32.6)	/	
COPD severity, n (%)				
Mild	540 (24.3)	540 (74.6)	/	
Moderate	155 (7.0)	155 (21.4)	/	
Severe/extremely severe	29 (1.3)	29 (4.0)	/	
COPD phenotype, n (%)				
Emphysema-predominant	75 (3.4)	75 (10.4)	/	
Nonemphysema-predominant	581 (26.1)	581 (80.2)	/	
Unclassified	68 (3.1)	68 (9.4)	/	

**Notes:** <sup>a</sup>Comparison between COPD and non-COPD. <sup>b</sup>Other subtypes including adenosquamous, carcinoma carcinoid tumors, sarcomatoid carcinoma, and pulmonary melanoma. /, not applicable.

**Abbreviations:** BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; LCLC, large cell lung cancer; SCLC, small cell lung cancer.

Multivariate Cox regression analysis showed that after adjustment for age, sex, BMI, smoking status, and therapy method, emphysema-predominant phenotype of moderate and severe COPD was significantly associated with the decreased OS of lung cancers (HR 1.96, 95% CI 1.12–3.46; HR 2.37, 95% CI 1.04–5.40). However, the presence of nonemphysema-predominant phenotype of any grades of COPD showed no impact on the prognosis of lung cancer.

Subgroup analysis indicated that there were some differences in the prognosis of lung cancer among histological subtypes (Figure 2). Further multivariate Cox regression

analysis stratified by histology demonstrated that after adjustment for age, sex, BMI, smoking status, and therapy method, emphysema-predominant phenotype of COPD was significantly associated with the decreased OS of squamous carcinoma (HR 2.53, 95% CI 1.49–4.30), while there was no other significant relationship between COPD phenotypes and the prognosis of adenocarcinoma, SCLC, LCLC, and other histologic subtypes. Besides, surgical treatment, after adjustment, was still significantly associated with the increased OS of squamous carcinoma and adenocarcinoma (HR 0.43, 95% CI 0.32–0.59; HR 0.42, 95% CI 0.30–0.60). We also

**Table 2** Characteristics of COPD phenotypes

Characteristics	Emphysema-predominant phenotype (n=75)	Nonemphysema-predominant phenotype (n=581)	P-value <sup>a</sup>
Age, years (mean ± SD)	63.5±7.9	62.4±8.6	0.291
Sex, n (%)			0.033
Male	71 (94.7)	505 (86.9)	
Female	4 (5.3)	76 (13.1)	
BMI, kg/m <sup>2</sup> (mean ± SD)	23.3±3.7	23.3±3.4	0.348
Smoking status, n (%)			0.082
Current and ex-smokers	46 (61.3)	407 (70.1)	
Nonsmokers	29 (38.7)	174 (29.9)	
FVC, L (mean ± SD)	2.9±0.8	3.3±0.7	<0.001
FVC% predicted, % (mean ± SD)	86.4±21.9	96.8±16.4	<0.001
FEV <sub>1</sub> , L (mean ± SD)	1.7±0.6	2.0±0.5	<0.001
FEV <sub>1</sub> predicted, % (mean ± SD)	64.4±23.6	77.6±14.6	<0.001
FEV <sub>1</sub> /FVC, % (mean ± SD)	56.6±10.8	62.5±5.4	<0.001
AC	128.6±7.0	151.2±7.2	<0.001
COPD severity, n (%)			
Mild	22 (29.3)	464 (79.9)	<0.001
Moderate	36 (48.0)	107 (18.4)	<0.001
Severe/extremely severe	17 (22.7)	10 (1.7)	<0.001
Histology, n (%)			
Squamous carcinoma	41 (54.7)	270 (46.5)	0.112
Adenocarcinoma	17 (22.7)	229 (39.6)	0.003
SCLC	11 (14.7)	46 (7.9)	0.048
LCLC	4 (5.3)	21 (3.6)	0.318
Other subtypes <sup>b</sup>	2 (2.7)	15 (2.6)	0.598
Treatment, n (%)			0.054
Surgery	50 (66.7)	442 (76.1)	
Nonsurgery	25 (33.3)	139 (23.9)	

**Notes:** <sup>a</sup>Comparison between emphysema-predominant phenotype and nonemphysema-predominant phenotype. <sup>b</sup>Other subtypes include adenosquamous, carcinoma carcinoid tumors, sarcomatoid carcinoma, and pulmonary melanoma.

**Abbreviations:** AC, airway collapse; BMI, body mass index; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; LCLC, large cell lung cancer; SCLC, small cell lung cancer.

found a weak but significant effect of BMI on the prognosis of adenocarcinoma, where high BMI was associated with the increased OS (HR 0.93, 95% CI 0.89–0.98, Table 5).

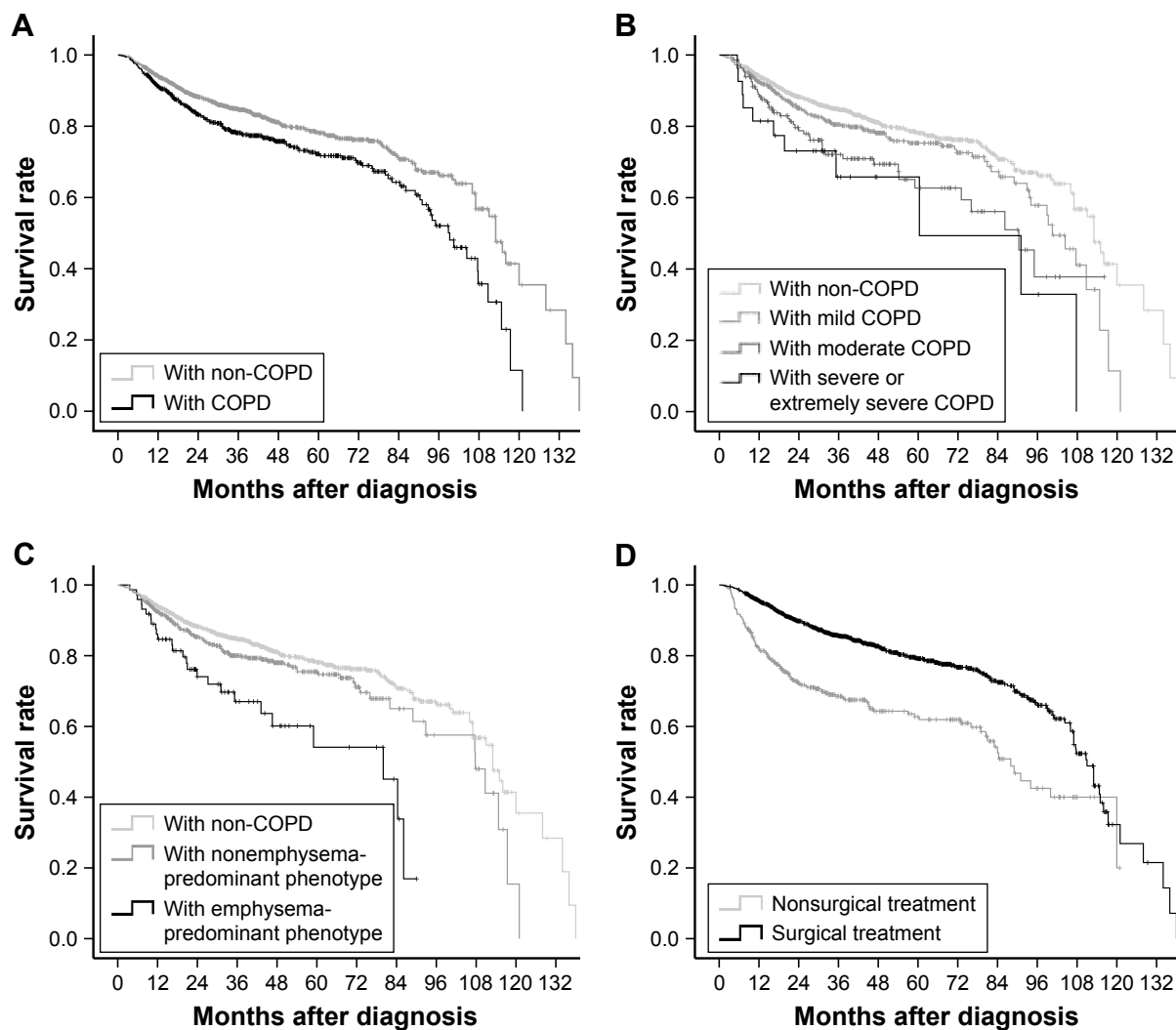
## Discussion

This study explored insight into the association between COPD phenotypes and the prognosis of specific lung cancer histological subtype. Our analysis revealed that after adjustment for age, sex, BMI, smoking status, and therapy method, COPD, especially emphysema-predominant phenotype, was an independent prognostic risk factor for squamous carcinoma. However, COPD and its phenotypes were not significantly associated with the prognosis of other common subtypes of lung cancer.

In recent decades, the treatment of lung cancer has achieved great medical advances, but the survival rate of lung cancer is still very low.<sup>2</sup> It is therefore important to identify factors related to the prognosis of lung cancer. Recently, COPD is considered to be a potential factor that

affects the development of lung cancer. Some studies have reported that COPD was closely related to the occurrence of lung cancer. A prospective study has revealed that the lung cancer incidence in COPD patients was up to 16.7 per 1,000 person-years.<sup>12</sup> Moreover, previous studies have reported that approximately 40%–70% of lung cancers coexist with COPD.<sup>13–15,18,29</sup> Results of our study revealed a high prevalence of COPD: 32.8% out of 2,222 lung cancer patients. This suggested that the lowest percentages published thus far has avoided overdiagnosis by self-reporting of COPD<sup>14</sup> and was not performed only in population who are at higher risk (eg, smokers and advanced age).<sup>13,15,30</sup> The prevalence of COPD in this study should be much closer to that in overall lung cancer population and was higher than that in social population.<sup>31</sup> However, the impact of COPD on the survival of patients with lung cancer remains ambiguous.

Some studies have reported that the presence of COPD showed an unfavorable effect on the survival of lung cancer patients,<sup>19,32,33</sup> but others disagree.<sup>20,29,34</sup> One of the important



**Figure 1** Kaplan–Meier curves of overall survival of lung cancer. **Notes:** (A) Overall survival curves stratified by COPD ( $P<0.001$ ). (B) Overall survival curves stratified by COPD severity ( $P<0.001$ ). (C) Overall survival curves stratified by COPD phenotype ( $P<0.001$ ). (D) Overall survival curves stratified by treatment method ( $P<0.001$ ).

**Table 3** HRs for overall survival according to clinicopathologic variables among lung cancer patients

Variables	Univariate analysis			Multivariate Cox regression <sup>a</sup>		
	HR	95% CI	P-value	HR	95% CI	P-value
COPD (present)	1.46	1.20–1.76	<0.001	1.28	1.05–1.57	0.016 <sup>b</sup>
COPD severity (increase)	1.35	1.20–1.53	<0.001	1.23	1.08–1.39	0.002 <sup>c</sup>
Emphysema-predominant phenotype (present)	2.45	1.63–3.67	<0.001	1.84	1.21–2.80	0.004 <sup>d</sup>
Nonemphysema-predominant phenotype (present)	1.27	1.03–1.59	0.029	1.11	0.91–1.43	0.265 <sup>e</sup>
Age (increase)	1.01	1.00–1.02	0.017	1.01	1.00–1.02	0.033 <sup>b</sup>
BMI (increase)	0.95	0.93–0.98	<0.001	0.96	0.94–0.99	0.003 <sup>b</sup>
Sex (female)	0.80	0.64–1.01	0.059	0.82	0.62–1.07	0.144 <sup>b</sup>
Smoking status (smokers)	1.04	0.86–1.26	0.658	0.88	0.71–1.10	0.263 <sup>b</sup>
Surgery (yes)	0.44	0.36–0.54	<0.001	0.46	0.37–0.56	<0.001 <sup>b</sup>

**Notes:** <sup>a</sup>There were four Cox regression models. COPD (dichotomous, referent: non-COPD), COPD grading (continuous, increase), emphysema-predominant phenotype of COPD (dichotomous, referent: non-COPD), and nonemphysema-predominant phenotype of COPD (dichotomous, referent: non-COPD) were, respectively, distributed in models 1, 2, 3, and 4. Age (continuous, increase), BMI (continuous, increase), sex (dichotomous, referent: male), smoking status (dichotomous, referent: nonsmoking), and surgery (dichotomous, referent: nonsurgery) were common variables of models 1–4; <sup>b</sup>Model 1; <sup>c</sup>Model 2; <sup>d</sup>Model 3; <sup>e</sup>Model 4.

**Abbreviation:** BMI, body mass index.

**Table 4** HRs for overall survival according to different phenotypes of different severities of COPD among lung cancer patients

COPD <sup>a</sup>	Univariate analysis			Multivariate Cox regression <sup>b</sup>		
	HR	95% CI	P-value	HR	95% CI	P-value
Total COPD						
Mild COPD	1.29	1.04–1.61	0.021	1.18	0.94–1.48	0.156
Moderate COPD	1.85	1.35–2.53	<0.001	1.52	1.10–2.10	0.012
Severe/extremely severe COPD	2.55	1.39–4.66	0.002	1.97	1.06–3.63	0.031
Emphysema-predominant phenotype						
Mild COPD	2.16	1.02–4.57	0.045	1.44	0.67–3.09	0.352
Moderate COPD	2.31	1.32–4.03	0.003	1.96	1.12–3.46	0.019
Severe/extremely severe COPD	3.38	1.50–7.62	0.003	2.37	1.04–5.40	0.040
Nonemphysema-predominant phenotype						
Mild COPD	1.15	0.90–1.47	0.249	1.07	0.83–1.37	0.622
Moderate COPD	1.70	1.15–2.52	0.008	1.38	0.92–2.07	0.118
Severe/extremely severe COPD	2.31	0.86–6.22	0.096	1.95	0.72–5.32	0.191

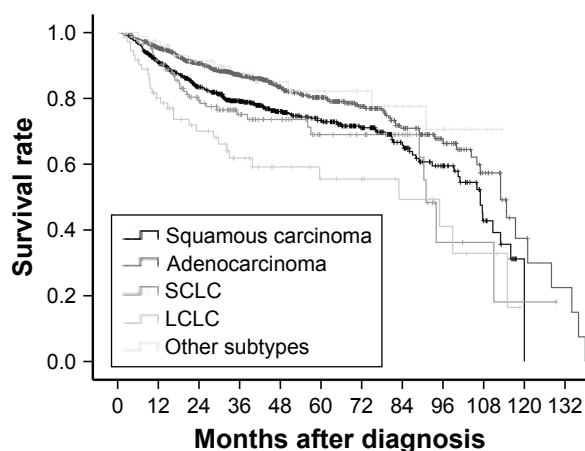
**Notes:** <sup>a</sup>Compared with non-COPD; <sup>b</sup>Adjusted by age (continuous), BMI (continuous), sex (dichotomous), smoking status (dichotomous), and surgery (dichotomous).

**Abbreviation:** BMI, body mass index.

limitations of previous studies was the enrollment of small number of lung cancer patients, which might be a potential explanation for these inconsistent results. Whereas in our large sample size study, the 5-year OS rates of lung cancers with COPD were significantly lower than that of lung cancers without COPD. The results were higher than the overall 5-year survival in overall lung cancer population<sup>2</sup> but were consistent with OS rates in patients undergoing surgery.<sup>19</sup> The reason for this was due to the involvement of early-stage (stage IA–IIB) lung cancers who were preparing for lung cancer surgery in this study. At last, >82% of them had undergone surgery. Moreover, we observed that patients with COPD had increased risk of worsened OS of lung cancer, after adjusting for age, sex, BMI, smoking status, and therapy method. The results were in line with another study conducted

in patients with early-stage NSCLC.<sup>33</sup> To the best of our knowledge, this is a study with the largest sample size that assessed the impact of COPD on OS of lung cancer.

It is well known that lung cancer and COPD are both heterogeneous diseases, and so there arises a question of whether there is any specific relationship between COPD phenotypes and the prognosis related to different histologic subtypes of lung cancer? Majority of the studies have been performed in NSCLC patients but were insufficient to provide enough information on histological subtypes. The cases in this study were collected over for a decade and included all common lung cancer subtypes. What is more, the proportion of each subtype was very close to the epidemiological distribution of lung cancer subtypes.<sup>35</sup> Lung cancers were categorized based on biopsy or operative histology, which was easier to identify compared with the classification of COPD phenotypes. Visual semiquantitative and quantitative CT assessments of emphysema are common methods to identify COPD phenotypes.<sup>36</sup> Whereas the hard obtainable CT images and complicated nature of the procedure of CT assessment limit its usage in retrospective clinical studies. However, PFT is routinely used for patients with chronic airway disease and for lung cancers undergoing preoperative evaluations, and the results and raw data are much easier to obtain. In addition, computer quantification of AC on MEFV curve has been proved to be an alternative method for predicting the presence of emphysema, which consequently facilitates the emphysema-predominant COPD phenotype determination.<sup>26–28</sup> In this study, we categorized COPD into emphysema-predominant phenotype and nonemphysema-predominant phenotype according to the computer quantification of AC. Our results were obtained on disease heterogeneity perspective, which



**Figure 2** Kaplan–Meier curves of overall survival of different histological subtypes of lung cancer.

**Note:** Overall survival curves stratified by histology ( $P < 0.001$ ).

**Abbreviations:** LCLC, large cell lung cancer; SCLC, small cell lung cancer.

**Table 5** Impact of COPD and COPD phenotypes on overall survival of lung cancer stratified by histology

Variables <sup>a</sup>	Squamous carcinoma <sup>b</sup>	Adenocarcinoma <sup>b</sup>	SCLC <sup>b</sup>	LCLC <sup>b</sup>	Other subtypes <sup>b</sup>
COPD (present) <sup>c</sup>	1.39 (1.03–1.88) <sup>#</sup>	1.29 (0.92–1.83) <sup>*</sup>	1.16 (0.60–2.23) <sup>*</sup>	0.84 (0.34–2.06) <sup>*</sup>	1.04 (0.29–3.75) <sup>*</sup>
COPD severity (increase) <sup>d</sup>	1.28 (1.07–1.53) <sup>#</sup>	1.21 (0.95–1.56) <sup>*</sup>	1.06 (0.74–1.52) <sup>*</sup>	0.88 (0.48–1.59) <sup>*</sup>	0.81 (0.29–2.29) <sup>*</sup>
Emphysema-predominant phenotype (present) <sup>e</sup>	2.53 (1.49–4.30) <sup>#</sup>	0.96 (0.30–3.06) <sup>*</sup>	0.84 (0.18–3.86) <sup>*</sup>	1.03 (0.21–4.96) <sup>*</sup>	4.67 (0.02–110) <sup>*</sup>
Nonemphysema-predominant Phenotype (present) <sup>f</sup>	1.09 (0.78–1.52) <sup>*</sup>	1.34 (0.92–1.94) <sup>*</sup>	1.01 (0.45–2.25) <sup>*</sup>	0.46 (0.13–1.62) <sup>*</sup>	1.09 (0.22–5.37) <sup>*</sup>
Age (increase) <sup>c</sup>	1.01 (0.99–1.03) <sup>*</sup>	1.01 (0.99–1.03) <sup>*</sup>	0.99 (0.96–1.03) <sup>*</sup>	1.01 (0.97–1.06) <sup>*</sup>	1.03 (0.97–1.10) <sup>*</sup>
BMI (increase) <sup>c</sup>	0.99 (0.95–1.03) <sup>*</sup>	0.93 (0.89–0.98) <sup>#</sup>	0.99 (0.91–1.08) <sup>*</sup>	0.90 (0.80–1.01) <sup>*</sup>	1.04 (0.92–1.18) <sup>*</sup>
Sex (female) <sup>c</sup>	1.32 (0.80–2.19) <sup>*</sup>	0.74 (0.50–1.09) <sup>*</sup>	1.48 (0.53–4.10) <sup>*</sup>	0.87 (0.23–3.23) <sup>*</sup>	1.47 (0.29–7.53) <sup>*</sup>
Smoking status (smokers) <sup>c</sup>	0.86 (0.62–1.21) <sup>*</sup>	0.82 (0.57–1.17) <sup>*</sup>	1.70 (0.67–4.32) <sup>*</sup>	0.33 (0.13–0.83) <sup>#</sup>	1.14 (0.25–5.29) <sup>*</sup>
Surgery (yes) <sup>c</sup>	0.43 (0.32–0.59) <sup>#</sup>	0.42 (0.30–0.60) <sup>#</sup>	0.60 (0.31–1.89) <sup>*</sup>	1.08 (0.37–3.18) <sup>*</sup>	0.78 (0.09–6.82) <sup>*</sup>

**Notes:** <sup>a</sup>There were four Cox regression models, and each lung cancer subtypes was analyzed, respectively. COPD (dichotomous, referent: non-COPD), COPD grading (continuous, increase), emphysema-predominant phenotype of COPD (dichotomous, referent: non-COPD), and nonemphysema-predominant phenotype of COPD (dichotomous, referent: non-COPD) were, respectively, distributed in models 1, 2, 3, and 4. Age (continuous, increase), BMI (continuous, increase), sex (dichotomous, referent: male), smoking status (dichotomous, referent: nonsmoking), and surgery (dichotomous, referent: nonsurgery) were common variables of models 1–4; <sup>b</sup>HR (95% CI); <sup>c</sup>Model 1; <sup>d</sup>Model 2; <sup>e</sup>Model 3; <sup>f</sup>Model 4; <sup>#</sup> $P < 0.05$ ; <sup>\*</sup> $P > 0.05$ .

**Abbreviations:** BMI, body mass index; LCLC, large cell lung cancer; SCLC, small cell lung cancer.

showed that COPD, especially the emphysema-predominant phenotype was significantly associated with worsened OS of squamous carcinoma. Also, there were no other significant relationships between COPD phenotypes and prognosis of adenocarcinoma, SCLC, LCLC, and other histologic subtypes. Zhai et al have indicated that the presence of COPD was associated with worsened survival outcomes in patients with squamous carcinoma.<sup>33</sup> Ueda et al have found that CT-diagnosed emphysema, but not airway obstruction, was associated with poor prognosis in smokers with early-stage lung cancer.<sup>37</sup> A prospective study conducted by Turner et al have also reported that lung cancer mortality was significantly associated with emphysema, but not with chronic bronchitis.<sup>16</sup> Gullón et al have also shown that emphysema was an adverse prognostic factor in NSCLC.<sup>38</sup> Adding to these, our results demonstrated that disease heterogeneity might be another important reason for the cause of inconsistency among previously reported research results. In addition, we demonstrated that other factors related to the prognosis of lung cancer, such as BMI, smoking, and therapy method, were also affected by the disease heterogeneity.

A problem still exists that should not be ignored. In this study, the prevalence of moderate and more severe COPD in emphysema-predominant phenotype was significantly higher than those in nonemphysema-predominant phenotype of COPD. Our study also found that the OS of lung cancer was gradually worsened with the increased severity of COPD. One could argue whether the effect of COPD phenotype on the prognosis of lung cancer should be attributed to COPD severity. In order to solve this argument, further analysis was performed and found that nonemphysema-predominant

phenotype, even those classified into moderate or more severe COPD, showed no significant effect on the prognosis of lung cancer. So, we emphasized the impact of COPD phenotype on the prognosis of lung cancer, which is more important than that of COPD severity.

The mechanisms through which COPD influence the prognosis of lung cancer still remain unclear. Chronic inflammation, DNA repair capacity, and abnormal apoptosis have been identified as potential common mechanisms.<sup>39–46</sup> Moreover, COPD was associated with several clinical comorbidities, which may also affect the prognosis of lung cancer.<sup>47</sup> Researchers have pointed out that the heterogeneous nature of these two diseases has hampered the research progress toward the mechanistic links between COPD and the occurrence of lung cancer.<sup>48,49</sup> Our evaluation suggests that the mechanistic link between COPD and the development of lung cancer was also affected by disease heterogeneity. Previous evidences indicated that our hypothesis was biologically plausible. It has been shown that the matrix metalloproteinase is widely upregulated in emphysema and is associated with the occurrence of lymphovascular invasion and postoperative recurrence of lung cancer.<sup>50</sup> So, lung cancer coexisting with emphysema is considered to be more aggressive. Schiavon et al have commented that compared with adenocarcinoma without COPD, adenocarcinoma with COPD tends to be less invasive.<sup>51</sup> Further studies from the perspective of disease heterogeneity are required for better understanding of the mechanistic link between COPD and the prognosis of lung cancer.

In addition to the strengths of this study, including the larger sample size, confirmed diagnosis of lung cancer and



COPD and a focus on disease heterogeneity, there are several limitations. First, this study could not provide the impact of COPD on the progression-free survival of lung cancer due to lack of relevant information. It remains uncertain regarding the impact of COPD on the recurrence of lung cancer. Second, the stage of lung cancer is one of the most important prognostic factors in the analyses of OS of lung cancer patients. The effect of lung cancer staging on lung cancer prognosis was not observed in this study. The reason for this might be that 92.8% of lung cancer patients were at early stage (stage IA–IIB) and the later stage was not the main reason for not receiving surgical treatment in this study. Moreover, we did not collect the information regarding the use of inhaled corticosteroids, which are commonly prescribed to COPD patients and also has a potential role in cancer prevention and outcomes.<sup>52–54</sup> Further, well-designed prospective studies are required to solve these problems.

## Conclusion

COPD, especially emphysema-predominant phenotype, was an independent prognostic risk factor for squamous carcinoma. However, COPD and its phenotypes were not significantly associated with the prognosis of adenocarcinoma, SCLC, LCLC, and other histologic subtypes. Results of this study provide important implications on the research of the mechanism between lung cancer and COPD and contributed to the clinical identification of patients with higher risk for lung cancer prognosis.

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## Disclosure

The authors report no conflicts of interest in this work.

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