

Status of coexisting chronic obstructive pulmonary disease and its clinicopathological features in patients undergoing lung cancer surgery: a cross-sectional study of 3,006 cases

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Background: Lung cancer is often complicated with chronic obstructive pulmonary disease (COPD). Coexistence of COPD has significant impacts on the decision-making process for lung cancer surgery as well as the postoperative effects. This study aimed to investigate the status of coexisting COPD and analyze its clinicopathological characteristics in lung cancer patients undergoing surgical resection.

Methods: Clinical data of 3,006 patients with resected primary lung cancer from January 2008 to April 2014 were analyzed. Status of coexisting COPD was evaluated according to patient's lung function. Differences of clinicopathological characteristics between the COPD group and the non-COPD group were compared.

Results: A total of 643 patients (21.4%) were complicated with COPD. The average age of patients with COPD (64.9±8.5 years) was significantly older than those without COPD (59.4±9.9 years). The percentage of males (85.7% vs. 54.0%) and current smokers (43.4% vs. 22.5%) were both higher in the COPD group than the non-COPD group (P<0.05). The percentage of patients with initial symptoms was higher in the COPD group than the non-COPD group (63.9% vs. 44.5%, P<0.05). The average white blood cell count was higher in the COPD group than the non-COPD group [(6.72±2.28 vs. 6.28±2.24) ×10⁹/L, P<0.05]. The percentage of tumor size more than 3 cm was higher in the COPD group than the non-COPD group (53.2% vs. 38.0%, P<0.05). Squamous cell carcinoma accounted for 47.6% in the COPD group while adenocarcinoma accounted for 72.4% in the non-COPD group (P<0.05). A higher percentage of lung cancer with poor differentiation was found in the COPD group than the non-COPD group (53.2% vs. 43.6%, P<0.05). The median total and postoperative length of hospital stay were significantly longer in the COPD group than the non-COPD group (13 vs. 11 days, 8 vs. 7 days, respectively, P<0.05).

Conclusions: COPD is a common comorbidity of early stage lung cancer. Lung cancer patients with coexistence of COPD have obviously different clinicopathological features compared to patients without COPD, which requires special attention and management during the perioperative period of lung cancer.

Keywords: Lung cancer; chronic obstructive pulmonary disease (COPD); surgery; clinicopathological feature

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Introduction

Lung cancer is the most common malignancy and remains the number one killer among all kinds of cancers worldwide (1). Over the past decades, due to tobacco consumption, environmental pollution and occupational exposure, the morbidity and mortality of lung cancer have been increasing dramatically in the world and especially in China (2). Chronic obstructive pulmonary disease (COPD) as another major respiratory disease is characterized by persistent inflammation in airways, leading to airflow limitation that cannot be completely reversed and progressive decline in lung function (3). During the last decade, increasing studies have shown that lung cancer and COPD are far from irrelevant: despite shared etiological factors such as cigarette smoking and air pollution, COPD is an independent risk factor for developing lung cancer. The risk of lung cancer in patients with COPD is two to six times higher than those without COPD (4). On the other hand, nearly 50–80% of patients diagnosed with lung cancer have existed COPD (5).

In recent years, even though great advances have been made in chemoradiotherapy and targeted therapy, curative surgery is still the most effective treatment for lung cancer at early stage (6). However, when surgical treatment comes to patients with operable lung cancer who have a coexistence of COPD, things are different. Patients with COPD have pre-existing impairment of lung function, which may fail to reach the respiratory evaluation standard required in lung resection (7), thus gaining relatively lower opportunities to receive lung cancer surgery (8). And worse still, a great number of studies demonstrated that even patients with impaired lung function could go through lung cancer surgery, an increased risk for postoperative complications such as pneumonia and persistent air leak would be another problem for them (9). Patients of lung cancer with coexistence of COPD had worse postoperative overall survival than patients without COPD (10,11), which can be partially attributed to the fact that COPD might accelerate lung cancer recurrence after surgery (12,13). Considering coexistence of COPD exerts seriously adverse impacts on lung cancer surgery and surgical curative effects, it is essential to investigate the status of coexisting COPD and figure out its clinicopathological characteristics in patients undergoing lung cancer surgery.

Methods

Patients

Clinical data of patients undergoing lung cancer surgery

in the department of thoracic surgery of Zhongshan Hospital of Fudan University from January 2008 to April 2014 were gathered from hospital records databases for this research. Inclusion criteria: patients with primary lung cancer which was pathologically confirmed after surgery. Exclusion criteria: patients with lung cancer diagnosed as metastasis due to primary tumors in other organs such as colorectal cancer and liver cancer; patients complicated with primary tumors in other organs simultaneously; patients who underwent lung resection for more than one time; patients who had received chemoradiotherapy before surgery; patients without complete clinical and pathological information. Finally, a total of 3,006 cases meeting the criteria above were selected for this study.

Clinicopathological parameters

Demographic and clinicopathological parameters gathered for this analysis included age, gender, smoking status, peripheral white blood cell (WBC) count, initial symptoms, tumor size measured by the largest diameter of lung cancer, histological subtype, histological differentiation, pathological TNM stage, surgical type, length of hospital stay and patient's post-bronchodilator lung functions such as forced expiratory volume in one second (FEV_1), ratio of FEV_1 to predicted values ($FEV_1\%$ pred), forced vital capacity (FVC), ratio of FVC to predicted values ($FVC\%$ pred), ratio of FEV_1 to FVC (FEV_1/FVC), ratio of residual volume to total lung capacity (RV/TLC), diffusion capacity for carbon monoxide of the lung-single breath (D_LCO-SB). All lung function values were preoperative. According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) standard for diagnosis and grade of COPD (14), patients with a post-bronchodilator $FEV_1/FVC < 70\%$ were defined as COPD ($FEV_1\%$ pred $\geq 80\%$ as mild-COPD; $50\% \leq FEV_1\%$ pred $< 80\%$ as moderate-COPD; $FEV_1\%$ pred $< 50\%$ as severe-COPD). Patients with $FEV_1/FVC \geq 70\%$ were defined as non-COPD. Clinicopathological parameters mentioned above were compared among the different groups.

Statistical analysis

Quantitative data were expressed as mean \pm SD (standard deviation) or median (interquartile range). Data with normal distribution were analyzed using one-way analysis of variance or Student's *t*-test. Data with abnormal distribution were analyzed using the nonparametric Mann-Whitney

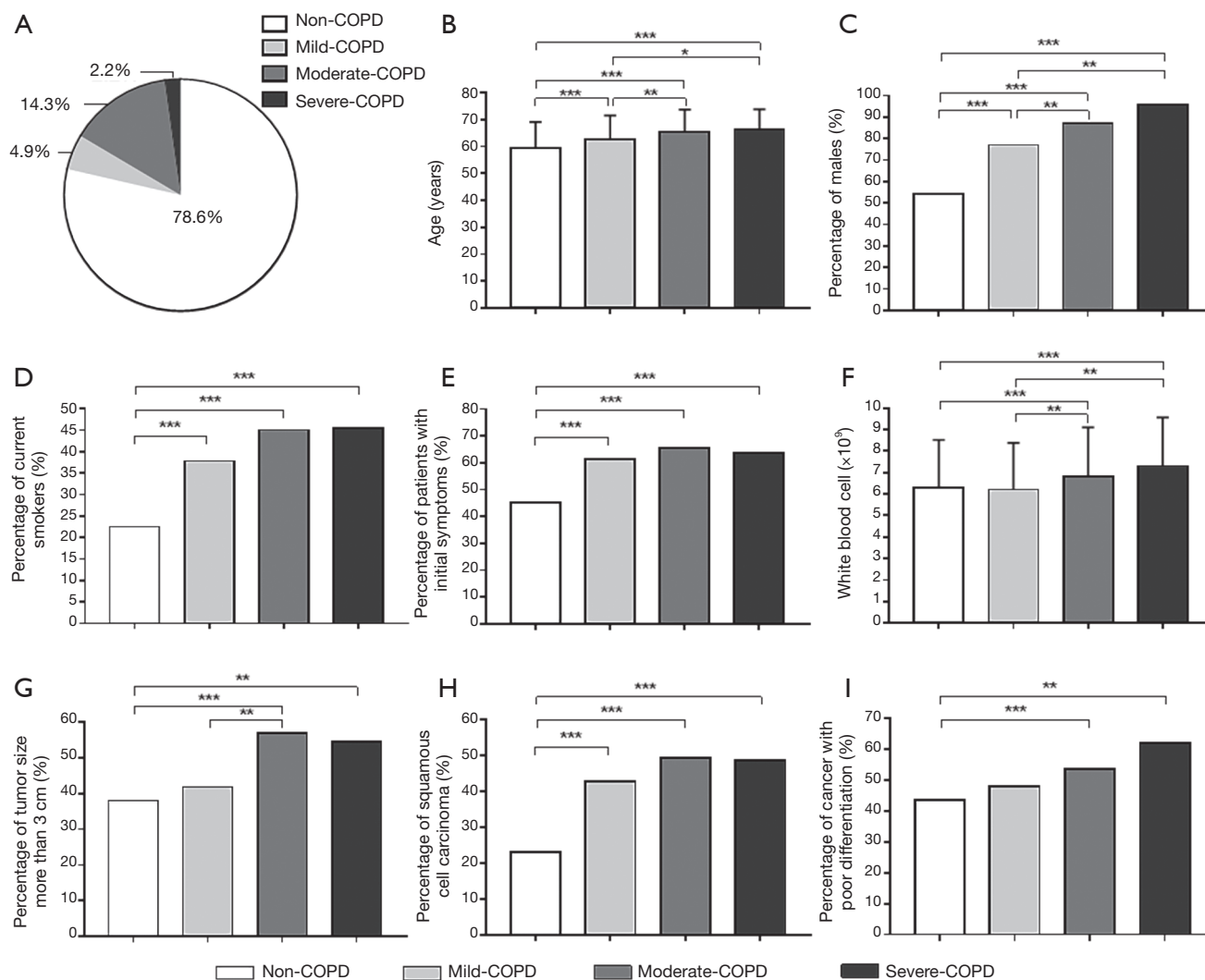


Figure 1 Comparison of clinicopathological characteristics between patients with different severities of COPD and without COPD. (A) Proportion of COPD with different severities; (B) comparison of age among the four groups; (C) comparison of percentages of males among the four groups; (D) comparison of percentages of current smokers among the four groups; (E) comparison of percentages of initial symptoms among the four groups; (F) comparison of WBC among the four groups; (G) comparison of percentages of tumor size more than 3cm among the four groups; (H) comparison of percentages of squamous cell carcinoma among the four groups; (I) comparison of percentages of cancer with poor differentiation among the four groups. ***, $P < 0.001$; **, $P < 0.01$; *, $P < 0.05$.

U test. Categorical data were expressed as percentages and analyzed using Chi-square test. Ranked data such as tumor stage were analyzed using the Mann-Whitney U test. Length of hospital stay were also analyzed using the Kaplan-Meier method with the log-rank test. All statistical analyses were performed by SPSS for Windows (Version 17.0, Chicago, IL, USA). All P values were two-sided and a difference was considered statistically significant at $P < 0.05$.

Results

Status of coexisting COPD

A total of 643 cases (21.4%) were complicated with COPD in 3,006 patients, of which 148 cases (4.9%) were mild COPD, 429 cases (14.3%) were moderate COPD and 66 cases (2.2%) were severe COPD (Figure 1A). Except for FVC (L), the differences of all other lung function

Table 1 Comparison of lung function between patients with and without COPD

Lung function	Total (n=3,006)	Non-COPD (n=2,363)	COPD (n=643)	P
FEV ₁ (L)	2.33±0.63	2.45±0.59	1.90±0.54	<0.001
FEV ₁ %pred (%)	87.30±18.69	92.43±15.95	68.45±15.73	<0.001
FEV ₁ %pred (%)	3.06±0.74	3.07±0.74	3.03±0.73	0.165
FVC%pred (%)	90.36±15.47	91.86±14.91	84.84±16.24	<0.001
FEV ₁ /FVC (%)	76.06±9.29	79.76±5.61	62.46±7.29	<0.001
D _L CO-SB	18.29±7.18	18.95±7.31	15.89±6.10	<0.001
RV/TLC (%)	37.17±9.64	36.05±9.21	41.27±10.09	<0.001

FEV₁, forced expiratory volume in 1s; FEV₁%pred, Ratio of FEV₁ to predicted values; FVC, forced vital capacity; FVC%pred, ratio of FVC to predicted values; FEV₁/FVC, ratio of FEV₁ to FVC; RV/TLC, ratio of residual volume to total lung capacity; DLCO-SB, diffusion capacity for carbon monoxide of the lung-single breath.

parameters between the COPD group and the non-COPD group were statistically significant ($P<0.05$). FEV₁, FEV₁%pred, FVC%pred, FEV₁/FVC and D_LCO-SB in the COPD group were significantly inferior to the counterparts in the non-COPD group ($P<0.05$), while RV/TLC presented the opposite trend ($P<0.05$), as presented in *Table 1*.

Comparison of clinicopathological characteristics between patients with and without COPD

As presented in *Table 2*. Patients with COPD (64.9±8.5 years) were significantly older than those without COPD (59.4±9.9 years). Males (85.7% *vs.* 54.0%) and current smokers (43.4% *vs.* 22.5%) were both markedly more in the COPD group than the non-COPD group ($P<0.05$). Patients with COPD presented significantly more initial symptoms than patients without COPD (63.9% *vs.* 44.5%, $P<0.05$), including cough or sputum, bloody sputum or hemoptysis, chest tightness or dyspnea and chest pain (all $P<0.05$) (*Table 3*). Patients with COPD were more likely to manifest two or more symptoms compared to those without COPD (23.2% *vs.* 14.0%, $P<0.05$) (*Table 3*). WBC count was higher in the COPD group than the non-COPD group [(6.72±2.28 *vs.* 6.28±2.24) ×10⁹/L, $P<0.05$].

As presented in *Table 2*. Patients with COPD were more likely to have bigger tumor with size more than 3 cm than patients without COPD (53.2% *vs.* 38.0%, $P<0.05$). Adenocarcinoma (72.4%) was the most common histological subtype in patients without COPD, while squamous cell carcinoma (47.6%) and adenocarcinoma (47.0%) happened similarly frequently in patients with COPD. A higher

percentage of lung cancer with poor differentiation was found in the COPD group than the non-COPD group (53.2% *vs.* 43.6%, $P<0.05$). However, the difference of tumor pathological stage between the COPD group and the non-COPD group was not significant ($P>0.05$).

As presented in *Table 2*. Although lobectomy was the predominant surgical type for patients with or without COPD, sub-lobectomy and sleeve resection were more frequent in the COPD group than the non-COPD group ($P<0.05$). The median total length of hospital stay was significantly longer in the COPD group than the non-COPD group (13 *vs.* 11 days, $P<0.05$), so was the median postoperative length of hospital stay (8 *vs.* 7 days, $P<0.05$).

Comparison of clinicopathological characteristics among patients with different severities of COPD and without COPD

Clinicopathological characteristics were further compared among the non-COPD group, the mild-COPD group, the moderate-COPD group and the severe-COPD group. Both age and percentage of males presented significantly increasing trend with declining of lung function, as shown in *Figure 1B,C*, respectively. Patients with COPD, no matter the grade of the severity, were all prone to be current smokers, as shown in *Figure 1D*. The percentage of patients with initial symptoms in the four groups above were 44.5%, 60.8%, 65.3% and 62.1%, respectively. Patients with COPD, no matter its severity, presented markedly more symptoms than patients without COPD, while no significant difference when compared within the mild, moderate and severe COPD groups ($P>0.05$), as shown in

Table 2 Comparison of clinicopathological characteristics between patients with and without COPD

Characteristic	Total (n=3,006)	Non-COPD (n=2,363)	COPD (n=643)	P
Age (years)	60.5±9.9	59.4±9.9	64.9±8.5	<0.001
Gender				<0.001
Male	1,827 (60.8)	1,276 (54.0)	551 (85.7)	
Female	1,179 (39.2)	1,087 (46.0)	92 (14.3)	
Smoking status				<0.001
Current	811 (27.0)	532 (22.5)	279 (43.4)	
Former or never	2,195 (73.0)	1,831 (77.5)	364 (56.6)	
Initial symptoms				<0.001
Yes	1,462 (48.6)	1,051 (44.5)	411 (63.9)	
No	1,544 (51.4)	1,312 (55.5)	232 (36.1)	
White blood cell ($\times 10^9/L$)	6.37±2.26	6.28±2.24	6.72±2.28	<0.001
Tumor size (cm)				<0.001
>3	1,241 (41.3)	899 (38.0)	342 (53.2)	
≤3	1,765 (58.7)	1,464 (62.4)	301 (46.8)	
Histological subtype				<0.001
Squamous cell	854 (28.4)	548 (23.2)	306 (47.6)	
Adenocarcinoma	2,013 (67.0)	1,711 (72.4)	302 (47.0)	
Others	139 (4.6)	104 (4.4)	35 (5.4)	
Histological differentiation				<0.001
Poor	1,372 (45.6)	1,030 (43.6)	342 (53.2)	
Well or moderate	1,634 (54.4)	1,333 (56.4)	301 (46.8)	
Pathological TNM stage				0.344
0 or I	1,862 (61.9)	1,484 (62.8)	378 (58.8)	
II	409 (13.6)	292 (12.4)	117 (18.2)	
III	666 (22.2)	527 (22.3)	139 (21.6)	
IV	69 (2.3)	60 (2.5)	9 (1.4)	
Surgical type				<0.001
Lobectomy	2,394 (79.6)	1,939 (82.1)	455 (70.8)	
Sub-lobectomy	247 (8.2)	179 (7.6)	68 (10.6)	
Bilobectomy	153 (5.1)	110 (4.7)	43 (6.7)	
Sleeve resection	133 (4.4)	83 (3.5)	50 (7.8)	
Pneumonectomy	79 (2.6)	52 (2.2)	27 (4.2)	
Length of hospital stay (days)				
Total	12 [9–14]	11 [9–14]	13 [10–16]	<0.001
Preoperative	4 [3–6]	4 [3–5]	4 [3–6]	0.001
Postoperative	7 [6–9]	7 [6–9]	8 [7–11]	<0.001

COPD, chronic obstructive pulmonary disease.

Table 3 Comparison of initial symptoms between patients with and without COPD

Initial symptoms	Total (n=3,006) (%)	Non-COPD (n=2,363) (%)	COPD (n=643) (%)	P
Cough or sputum	1,029 (34.2)	740 (31.3)	289 (44.9)	<0.001
Bloody sputum or hemoptysis	510 (17.0)	347 (14.7)	163 (25.3)	<0.001
Chest tightness or dyspnea	172 (5.7)	119 (5.0)	53 (8.2)	0.002
Chest pain	204 (6.8)	148 (6.3)	56 (8.7)	0.029
≥2 above	479 (15.9)	330 (14.0)	149 (23.2)	<0.001

Several different initial symptoms may be concurrently manifested on one patient.

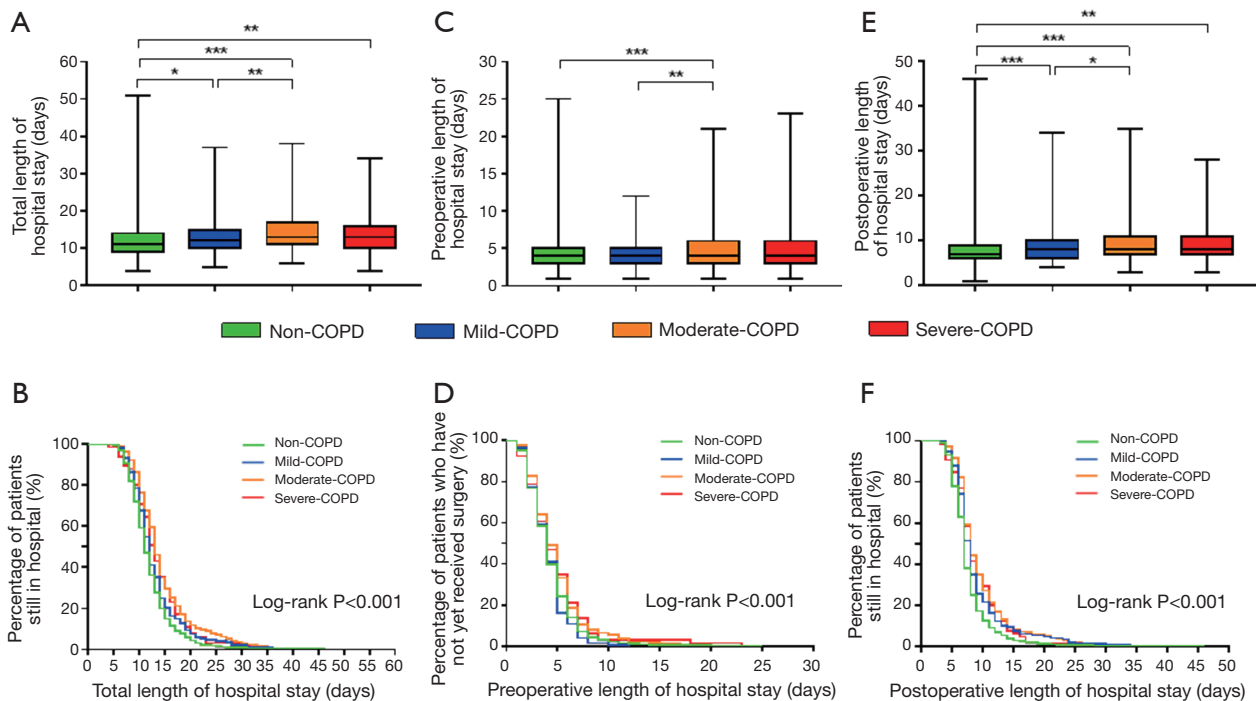


Figure 2 Comparison of length of hospital stay between patients with different severities of COPD and without COPD. (A) Comparison of median total length of hospital stay among the four groups; (B) Kaplan-Meier curves showing total length of hospital stay of the four groups; (C) comparison of median preoperative length of hospital stay among the four groups; (D) Kaplan-Meier curves showing preoperative length of hospital stay of the four groups; (E) comparison of median postoperative length of hospital stay among the four groups; (F) Kaplan-Meier curves showing postoperative length of hospital stay of the four groups. ***, $P < 0.001$; **, $P < 0.01$; *, $P < 0.05$.

Figure 1E. WBC count in patients with mild COPD was similar to that of patients without COPD, while WBC count in patients with moderate to severe COPD started to increase significantly as compared to patients without COPD ($P < 0.05$), but no further significantly higher as more severity of COPD, as shown in *Figure 1F*.

Patients with moderate and severe COPD significantly had bigger tumor, size more than 3 cm, than patients without COPD or just with mild COPD, with percentage

more than half, as shown in *Figure 1G*. Squamous cell carcinoma in patients without COPD was much less than patients with COPD, while no significant difference among the COPD groups with different severities ($P > 0.05$), as shown in *Figure 1H*. Patients with moderate and severe COPD but not mild COPD had significantly higher percentages of cancer with poor differentiation than patients without COPD ($P < 0.05$), as shown in *Figure 1I*.

As shown in *Figure 2A*. The median total length of

hospital stay in the four groups above were 11 [9–14] days, 12 (10–14.75) days, 13 [11–17] days and 13 [10–16] days, which significantly gradually increased by one day from patients without COPD to patients with mild-COPD and then to patients with moderate or severe COPD ($P<0.05$). And this result was also demonstrated through the nearly entire overlap of the orange curve indicating the moderate-COPD and the red curve indicating the severe-COPD, which was, however, separated from the blue curve indicating the mild-COPD and the green curve indicating the non-COPD at intervals of one day with the log-rank $P<0.001$, as shown in *Figure 2B*.

As shown in *Figure 2C*. The median preoperative length of hospital stay in the four groups above were 4 [3–5], 4 [3–5], 4 [3–6] and 4 [3–6] days. Only patients with moderate COPD have longer preoperative length of hospital stay than patients with mild COPD or without COPD. And this result can be also partially demonstrated through the nearly entire overlap of the orange curve indicating the moderate-COPD and the red curve indicating the severe-COPD, which was, however, partially separated from the nearly entire overlap of the blue curve indicating the mild-COPD and the green curve indicating the non-COPD with the log-rank $P<0.001$, as shown in *Figure 2D*.

As shown in *Figure 2E*. The median postoperative length of hospital stay in the four groups above were 7 [6–9] days, 8 [6–10] days, 8 [7–11] days and 8 [7–11] days. Much similarly to the result from total length of hospital stay, the median postoperative length of hospital stay significantly gradually increased by one day from patients without COPD to patients with mild-COPD and then to patients with moderate or severe COPD ($P<0.05$). And this result was also demonstrated through the nearly entire overlap of the orange curve indicating the moderate-COPD and the red curve indicating the severe-COPD, which was, however, separated from the blue curve indicating the mild-COPD and the green curve indicating the non-COPD with the log-rank $P<0.001$, as shown in *Figure 2F*.

Discussion

To date, although it has been well established that coexistence of COPD not only reduces operative chance but also increases postoperative complications and promotes cancer recurrence, which imposes seriously unfavorable impacts on prognosis of lung cancer patients after surgical resection (8–13), the status of coexisting COPD in patients with lung cancer is still substantially unnoticed by clinicians

and especially by thoracic surgeons (15,16). It was reported that even for patients with coexistence of COPD, different severities of COPD carried different risks for postoperative complications and patients with different severities of COPD showed disparate survival after lung cancer surgery (17). Hence, it is worth mentioning that different severities of COPD should be grouped in clinical study. In the present study, we showed that about 21.4% of patients undergoing lung cancer surgery had coexistence of COPD, among whom moderate-COPD was the most frequent, followed by mild and severe COPD, which implied less benefits they might obtain from the surgery and more attention should be paid to this specific population.

Our study demonstrated that more male elder patients were with coexistence of COPD, which were gradually increased with the severity of COPD. Patients with coexistence of COPD, no matter how severe the COPD was, were all prone to be current smokers. Zhai (18) and colleagues reported that cigarette smoking was the most important risk factor for developing lung cancer combined with COPD, especially in females and those with histology of squamous cell carcinoma.

Our study also found that patients with coexistence of COPD were more vulnerable to respiratory initial symptoms responsible for a clinical visit. In addition to smoking, we hypothesized reasons for this phenomenon might be: patients with COPD preexist narrowed airways and mucus hypersecretion (19), subsequent neoplasm formation in airways could be easily to trigger irritating cough or sputum; secondly, as shown in our study, lung cancer with COPD was often bigger in size and poorer in differentiation, which might grow faster and more easily completely obstruct airways to cause more frequent shortness of breath, chest tightness or dyspnea; thirdly, lung cancer with COPD, which is highly malignant and in a rapid growth condition, may be easier to generate tumor necrosis or invasion to surrounding micro-vessels, which resulted in more frequent bloody sputum or hemoptysis.

COPD is not only a respiratory inflammatory disease but also a systemic inflammatory disorder (20). WBC count, a biomarker measuring the systemic inflammatory level, is closely related to the severity of COPD (21). And it has been shown that the preoperative WBC count was an independent risk factor for postoperative cardiopulmonary complications after lobectomy for lung cancer (OR = 1.451, 95% CI: 1.212–1.736) (22). A persistent high level of systemic inflammation may increase the risk for postoperative pneumonia in patients undergoing lung

cancer surgery (23). Our study showed that WBC count in patients with COPD was significantly higher than those without COPD, consistent with the previous studies indicating that coexistence of COPD would increase postoperative complications after lung cancer surgery (9,24). Furthermore, we found that only patients with moderate or severe COPD but not mild COPD had a significantly higher WBC compared to those without COPD, consistent with the previous study indicating that only moderate or severe COPD was associated with increased postoperative pulmonary complications (11).

In the present study, it was obviously demonstrated that the total length of hospital stay was gradually increased at intervals of one day with the aggravating severity of COPD, which can be mainly attributed to the extended postoperative length of hospital stay. To some extent, the poorer lung function shown in our study and the more postoperative complications of patients with coexistence of COPD shown by others (9,11) may be responsible for this prolonged length of hospital stay. At last, from what has been discussed above, we easily found that all comparisons of clinicopathological parameters between patients with moderate COPD and patients with severe COPD were not statistically different, indicating that they indeed owned extremely similar clinicopathological characteristics. From this point, it is possible that we could gather up the moderate COPD and the severe COPD but separate the mild COPD for analysis in future clinical study.

In a word, the clinicopathological features of lung cancer combined with COPD are significantly distinguished from the counterparts of lung cancer alone, thoracic surgeons should attach great importance to coexistence of COPD and be familiar with its clinicopathological features in patients undergoing lung cancer surgery. With the help of pulmonologists, physicians who are really professional in COPD management (25), the status of coexisting COPD should be accurately diagnosed and adequately treated during the perioperative period of lung cancer.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the ethics committee of Zhongshan Hospital, Fudan University.

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