

Impact of Chronic Obstructive Pulmonary Disease on the Mortality of Patients with Small Cell Lung Cancer

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Background: Limited studies have focused on the impact of the coexistence of small cell lung cancer (SCLC) and chronic obstructive pulmonary disease (COPD). The study was to examine the impact of COPD on mortality in SCLC patients.

Methods: We analyzed SCLC patients from the Taiwan Cancer Registry Database between January 1, 1997, and December 31, 2015. The COPD population was composed of patients with a COPD diagnosis before the diagnosis of SCLC. The control group was composed of randomly selected SCLC patients without COPD who were propensity score matched with those with concomitant COPD according to age, sex, index date, cancer staging and comorbidities at a 1:1 ratio.

Results: Among 9425 SCLC patients in the database, eligible subjects were divided into the COPD group (n = 4235) and the non-COPD group (n = 2334). Compared to patients in the non-COPD group, the patients in the COPD group were older (71.4 versus 65.7 years, p<0.0001), had a lower percentage of stage IV disease (60.1% versus 68.3%, p<0.0001) and had more comorbidities. After matching, there were 1457 patients in each group. Older age, lower body mass index (BMI), and some comorbidities were associated with higher mortality, and comorbid COPD was associated with lower 1-year mortality in SCLC patients. Multivariate analysis identified older age, lower BMI, and concomitant congestive heart failure or diabetes as risk factors for OS.

Conclusion: A diagnosis of COPD was associated with reduced 1-year mortality in SCLC patients, but no significant difference after 1-year in this population.

Keywords: chronic obstructive pulmonary disease, small cell lung cancer

Introduction

Chronic obstructive pulmonary disease (COPD) is a common and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation. Data from the World Health Organization indicated that COPD was the third leading cause of death worldwide in 2019.¹ COPD is not only a pulmonary inflammation-related disease but also a systemic inflammatory disease and is associated with many systemic comorbidities. Previous studies indicated the significantly higher risk of cancer in patients with COPD than in those without COPD, and the most common cancer in this population was lung cancer.^{2,3} Our previous study showed that COPD status was associated with a twofold increase in lung cancer incidence.³ The tight association between COPD and lung cancer results from some common risk factors, such as age and cigarette smoking. Other mechanisms, including

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chronic inflammation in COPD, lead to tumorigenesis through increased expression of growth factors and over-expression of the transcription factor STAT3.⁴

Lung cancer, including small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), is the leading cause of cancer death worldwide. The prevalence of COPD is high in both SCLC and NSCLC patients and vice versa.^{5,6} COPD has been reported to play an important role in the prognosis of SCLC and NSCLC. Lee et al compared the clinical characteristics of patients with NSCLC concomitant with COPD and found that there was no impact of COPD on the mortality of patients with NSCLC.⁷ Tammemagi et al found that COPD was a significant predictor of survival variation in early- and late-stage SCLC and NSCLC patients.⁸ A meta-analysis conducted by Gao et al concluded that the presence of COPD and emphysema were predictors of poor prognosis in SCLC and NSCLC patients, but significant heterogeneity across their studies included patient characteristics, tumor staging, histologic types and different study designs and did not enroll patients with advanced (III–IV) stages.⁹ Tan et al conducted another systematic review and meta-analysis to evaluate the prognosis in patients with COPD and NSCLC following pulmonary resection and found that COPD increased mortality in patients with lung cancer following resection.¹⁰ Wu et al investigated the effect of NSCLC concomitant with COPD on prognosis and indicated that COPD has a deleterious effect on survival.¹¹ Mostly of those studies were focused on NSCLC, and studies investigating the prognostic significance of COPD for SCLC patients are limited. In addition, previous studies focused on the association of lung cancer and COPD were mainly in Caucasian populations, relevant data in Asian populations was scanty. Thus, we conducted a nationwide population-based study from the cancer registry of Taiwan's National Health Insurance Research Database (NHIRD) to investigate the impact of COPD on the survival of patients with SCLC in Asian populations.

Methods

Database

Study Cohort and Observation of Outcomes

Adult patients aged 20 years and older who were diagnosed with SCLC between 1 January 2000 and 31 December 2015 were identified from the cancer registry database of the NHIRD in Taiwan. Patients were excluded

from this study if they had been diagnosed with other types of cancer, other catastrophic illnesses (defined by the Ministry of Health and Welfare in Taiwan),¹² or COPD within 3 months or after their lung cancer diagnosis. The index date was defined as the date of lung cancer diagnosis. These patients were divided into two cohorts on the basis of COPD. The COPD cohort was composed of patients with a COPD diagnosis evidenced by at least three outpatient claims or at least one inpatient claim who needed at least one bronchodilator prescription at least 3 months before the diagnosis of SCLC. Patients without a diagnosis of COPD composed the “non-COPD cohort”. The comorbidities of the subjects in both cohorts were recorded using the ICD-10 version of Charlson comorbidity index before or on the index day. This study was approved by the institutional review board of E-Da Hospital (EMRP-108-061). Because patients' data could not be identified, the requirement for informed consent was waived.

Statistical Analysis

Clinical demographic data of the COPD and non-COPD cohorts were analyzed. These data included age, sex, cancer stage, body mass index (BMI), smoking (including former and current smokers), and associated comorbidities. Time to death was defined as the period from the index date to the death date. The results of subjects who were still living at the end of the follow-up period or were excluded from the database within the follow-up period were censored. The control group was composed of randomly selected SCLC patients without COPD after propensity score matching with SCLC patients with COPD according to age, sex, index date, cancer stage and comorbidities at a 1:1 ratio. After adjusting for age, sex, cancer stage, BMI, smoking, and associated comorbidities, the cumulative survival hazard ratios (HRs) for the two cohorts were calculated in accordance with the Cox proportional hazards regression model. Data were analyzed with SAS software for Windows, version 9.4 (SAS institute Inc., Cary, NC, USA). A two-sided p-value of 0.05 was considered statistically significant.

Results

A total of 9425 SCLC patients were identified in the database. As shown in [Figure 1](#), after excluding ineligible subjects, we included 4235 patients in the COPD

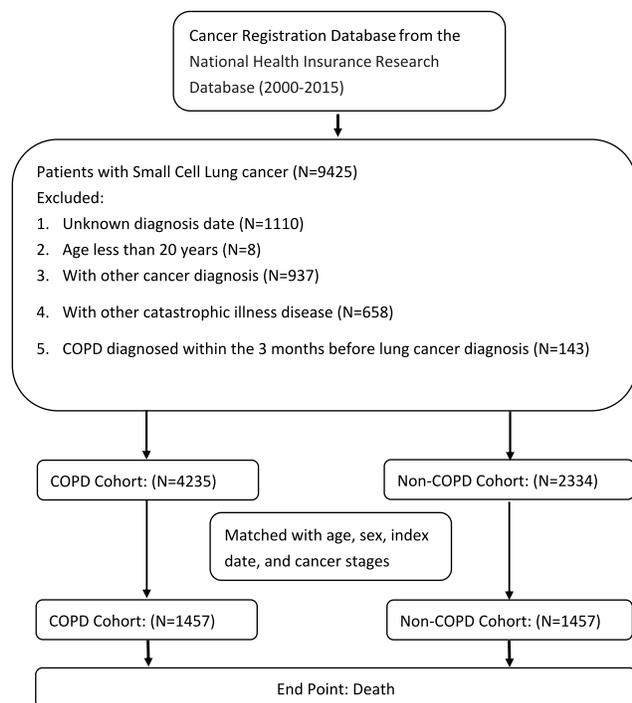


Figure 1 Flowchart of the study patients with newly diagnosed small cell lung cancer with and without COPD.

cohort and 2334 patients in the non-COPD cohort. The baseline characteristics of the study population are presented in Table 1. Compared to the non-COPD patients, the COPD patients were older (71.4 versus 65.7 years, $p < 0.0001$), had a lower percentage of stage IV disease (60.1% versus 68.3%, $p < 0.0001$) and had more comorbidities. After propensity score matching, as shown in Table 2, 1457 patients in each group were included in further analyses. Table 3 demonstrates the factors associated with survival after matching. Older age (HR: 1.02, CI: 1.03–1.04, $p < 0.0001$), stage IV disease (HR: 2.80, CI: 1.05–7.48, $p = 0.0397$), lower BMI (HR: 0.94, CI: 1.03–1.04, $p < 0.0001$), and certain comorbidities were associated with higher mortality. Comorbid COPD was associated with lower mortality in SCLC patients (HR: 0.89, CI: 0.83–0.96, $p = 0.0018$). However, multivariable Cox proportional analysis identified that only older age, lower BMI, and comorbidities of congestive heart failure (CHF) or diabetes were risk factors for OS.

Figure 2 illustrates the survival curves of SCLC patients with and without COPD. The cumulative

incidences of mortality between the non-COPD and COPD cohorts were statistically significant (74.0% vs 70.0%, $p = 0.0011$) at 1 year but no more significant after 1 year (93.0% vs 91.0% at 2 years, 96.4% vs 95.0% at 3 years and 97.7% vs 97.0% at 5 years, respectively).

Discussion

Our study indicated that comorbid COPD was associated with higher 1-year survival in patients with SCLC, whereas older age, lower BMI, stage IV disease, and comorbidities of CHF or diabetes were associated with a lower survival in these patients. After multivariate analysis, however, only age, BMI, and comorbid CHF or diabetes were risk factors for mortality.

Previous studies have examined the effect of COPD on the prognosis of lung cancer; however, most of those studies focused on operable lung cancer or NSCLC.^{7–11,13} A meta-analysis of 26 studies conducted by Gao et al indicated that the presence of COPD and emphysema are robust predictors of poor survival in patients with lung cancer.⁹ Recently, Wu et al conducted a meta-analysis with 12 case-control studies and showed that patients with NSCLC concomitant COPD was associated with poorer OS than the absence of COPD.¹¹

Few studies have investigated the impact of COPD on SCLC. Aarts et al conducted a large-scale, population-based study in Netherlands to survey the trends of comorbidities and their prognostic impact in patients with SCLC from 1995 to 2012.¹⁴ They reported that pulmonary diseases (included obstructive, restrictive pulmonary disease, lung fibrosis, and lung transplantation) were one of the most prevalent and increasingly common comorbid diseases. However, after multivariate analysis, they concluded that only digestive and cardiac disease in the limited stage and cardiac and cerebrovascular disease in the extensive-stage disease affected the prognosis. The results were consistent with our current study, which demonstrated that comorbid CHF and diabetes were associated with a poor outcome.

Ju et al retrospectively enrolled 110 Korean SCLC patients and categorized them into COPD ($n = 57$) or non-COPD ($n = 53$) groups according to the results of pulmonary function testing. Their multivariate analysis showed that only extensive-stage SCLC and poor performance

Table 1 Baseline Characteristics of the Study Population

	Non-COPD N=2334	COPD N=4235	p-value
Age	65.69±11.47	71.37±10.68	<0.0001
Age group, years			<0.0001
20–59	746 (31.96)	675 (15.94)	
60–75	1045 (44.77)	1800 (42.5)	
>75	543 (23.26)	1760 (41.56)	
Sex			0.1473
Male	2087 (89.42)	3834 (90.53)	
Female	247 (10.58)	401 (9.47)	
Lung cancer stage			<0.0001
Stage 1	23 (0.99)	112 (2.64)	
Stage 2	22 (0.94)	63 (1.49)	
Stage 3	477 (20.44)	1061 (25.05)	
Stage 4	1595 (68.34)	2547 (60.14)	
Unknown	217 (9.3)	452 (10.67)	
BMI	23.41±3.78	23.59±3.93	0.2294
Smoking (former and current)	2143 (91.82)	3954 (93.36)	
Follow-up period (mean±SD, years)	0.92±1.25	0.94±1.24	
Comorbidities			
Congestive heart failure	95 (4.07)	542 (12.8)	<0.0001
Peripheral vascular disease	64 (2.74)	214 (5.05)	<0.0001
Cerebrovascular disease	387 (16.58)	1078 (25.45)	<0.0001
Dementia	53 (2.27)	182 (4.30)	<0.0001
Connective tissue disease	25 (1.07)	122 (2.88)	<0.0001
Peptic ulcer disease	756 (32.39)	2025 (47.82)	<0.0001
Chronic liver disease	326 (13.97)	752 (17.76)	0.0001
Diabetes	563 (24.12)	1176 (27.77)	0.0013
Old cerebrovascular disease	50 (2.14)	101 (2.38)	0.5300
Chronic kidney disease	137 (5.87)	442 (10.44)	<0.0001
Death	2239 (95.93)	4077 (96.27)	0.4938

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.

status were independent risk factors for shorter OS. They concluded that coexisting COPD had no negative impact on the survival of patients with SCLC.¹⁵ In this nationwide, large-scale cohort study, although comorbid COPD was associated with lower mortality at 1 year, we observed a relative lower percentage of stage IV disease (60% versus 68% in non-COPD group) in this population, probable due to the relatively earlier diagnosis of SCLC in COPD patients who already receive treatment and regular follow-up in health facilities. Nevertheless, the mortality of SCLC patients with COPD was similar to that of patients without COPD after 1 year of diagnosis, probably

due to the high mortality of SCLC, and less than 10% of patients survived 2 years or longer.

The stage at presentation is one of the most important prognostic factors in patients with SCLC. Other clinical parameters in present study, such as performance status (PS), BMI, and comorbidities, also have prognostic importance in SCLC patients. A retrospective study indicated that age, BMI, and stage, but not COPD, were associated with the mortality of Korean patients with NSCLC, which was similar to the findings of our study.⁷ The prevalence of comorbidities is also high and has a substantial impact on prognosis in SCLC patients. A retrospective study in

Table 2 Baseline Characteristics of the Matched Study Population

	Non-COPD N=1457	COPD N=1457	p-value
Age	68.67±9.84	68.98±9.83	0.4007
Age group, years			0.7251
20–59	307 (21.07)	290 (19.90)	
60–75	723 (49.62)	738 (50.65)	
>75	427 (29.31)	429 (29.44)	
Sex			>0.9999
Male	1399 (96.02)	1399 (96.02)	
Female	58 (3.98)	58 (3.98)	
Lung cancer stage			>0.9999
Stage 1 and 2	6 (0.41)	6 (0.41)	
Stage 3	279 (19.15)	279 (19.15)	
Stage 4	1085 (74.47)	1085 (74.47)	
Unknown	87 (5.97)	87 (5.97)	
Follow-up period (mean±SD, years)	0.80±1.09	0.90±1.15	
BMI	23.31±3.65	23.89±3.95	0.0040
Smoking (former and current)	1356 (93.07)	1370 (94.03)	0.2911
Comorbidities			
Congestive heart failure	64 (4.39)	158 (10.84)	<0.0001
Peripheral vascular disease	50 (3.43)	72 (4.94)	0.0419
Cerebrovascular disease	290 (19.90)	334 (22.92)	0.0469
Dementia	42 (2.88)	45 (3.09)	0.7440
Connective tissue disease	15 (1.03)	31 (2.13)	0.0174
Peptic ulcer disease	497 (34.11)	657 (45.09)	<0.0001
Chronic liver disease	193 (13.25)	272 (18.67)	0.0001
Diabetes	371 (25.46)	422 (28.96)	0.0338
Old cerebrovascular disease	37 (2.54)	31 (2.13)	0.4616
Chronic kidney disease	102 (7.00)	134 (9.20)	0.0298
Death	1419 (97.39)	1410 (96.77)	0.3218

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Canada reviewed 174 patients with limited-stage SCLC and reported that increasing age was associated with decreased PS and increased comorbidity, but only poor PS was an independent prognostic factor associated with survival.¹⁶ The contrasting results might be explained by the relatively small sample size and enrollment of only limited-stage SCLC patients. In this large-scale study, age was still an independent risk factor for mortality.

Diabetes mellitus is one of the most common comorbidities in SCLC and NSCLC patients. However, the prognostic effect of diabetes in those lung cancer patients is inconclusive. An earlier study conducted in Norway reported prolonged survival in SCLC and NSCLC patients

with diabetes mellitus; however, a low prevalence of diabetes in the study population (only 84 of 1852 patients) might indicate selection bias.¹⁷ Similar to our present study, two retrospective studies in China and Turkey demonstrated that diabetes was a poor prognostic factor for surgically treated and advanced NSCLC patients.^{18,19} In addition, Kurishima et al studied 1798 Japanese patients with lung cancer, and 338 (18.8%) were comorbid with diabetes; they concluded that poorer PS, stage IV disease, SCLC pathology, and diabetes were poor prognostic factors for lung cancer.²⁰ However, a retrospective study in Turkey reviewed 161 SCLC patients with a focus on diabetes and other prognostic variables reported that

Table 3 Multivariable Cox Proportional Hazards Model Analysis for the Risk of Death

	Univariate	p-value	Multivariate	p-value
	HRs		HRs	
COPD vs Non-COPD	0.89 (0.83–0.96)	0.0018	0.92 (0.82–1.02)	0.1214
Age	1.04 (1.03–1.04)	<0.0001	1.03 (1.02–1.04)	<0.0001
Male vs Female	0.93 (0.77–1.12)	0.4292	1.27 (0.97–1.67)	0.084
Lung cancer stages				
Stage 1	0.28 (0.23–0.34)	<0.0001	0.19 (0.13–0.26)	<0.0001
Stage 2	0.35 (0.28–0.45)	<0.0001	0.28 (0.19–0.41)	<0.0001
Stage 3	0.51 (0.48–0.55)	<0.0001	0.47 (0.43–0.52)	<0.0001
Stage 4	REF.		REF.	
Unknown	0.69 (0.63–0.75)	<0.0001	0.61 (0.42–0.90)	0.0121
BMI	0.94 (0.93–0.96)	<0.0001	0.95 (0.93–0.96)	<0.0001
Smoking (former and current)	0.92 (0.79–1.07)	0.2709	1.04 (0.87–1.25)	0.6447
Comorbidities				
Congestive heart failure	1.46 (1.27–1.68)	<0.0001	1.35 (1.11–1.64)	0.0024
Peripheral vascular disease	1.41 (1.18–1.70)	0.0002	1.22 (0.91–1.63)	0.1746
Cerebrovascular disease	1.35 (1.24–1.48)	<0.0001	1.13 (0.97–1.30)	0.1086
Dementia	1.76 (1.42–2.19)	<0.0001	1.36 (0.97–1.91)	0.0722
Connective tissue disease	0.92 (0.68–1.24)	0.5908	0.83 (0.57–1.22)	0.3491
Peptic ulcer disease	1.10 (1.02–1.19)	0.0126	0.96 (0.85–1.07)	0.4363
Chronic liver disease	0.98 (0.89–1.08)	0.6853	0.97 (0.83–1.13)	0.6976
Diabetes	1.19 (1.10–1.30)	<0.0001	1.25 (1.08–1.44)	0.0022
Old cerebrovascular disease	1.31 (1.03–1.67)	0.0288	1.13 (0.75–1.71)	0.5625
Chronic kidney disease	1.39 (1.22–1.59)	<0.0001	1.19 (0.98–1.44)	0.0772

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HRs, hazard ratios.

diabetes at the time of diagnosis of SCLC did not have prognostic importance for survival.²¹ This results was discordant to our study, probably due to the relatively small sample size compared to ours. Physicians should increase awareness to recognize the associated comorbidities, including cardiovascular disease and diabetes, when providing patient care because the coexistence of comorbidities requires the integration of multiple disciplines and awareness of drug-drug interactions during cancer treatment.

A major limitation of our study is the lack of information on pulmonary function tests in the cancer registry data of the NHIRD, which may limit the diagnostic accuracy of COPD. However, we identified COPD patients with at least three outpatient claims or at least one inpatient claim coded who needed at least one bronchodilator prescription to minimize the rate of misdiagnosis. We also included

patients with a diagnosis of COPD at least 3 months before the diagnosis of SCLC to minimize the miscoding and prescription of bronchodilators simply for symptom relief. We were not able to perform a severity-adjusted comparison in patients according to COPD severity and PS due to the unavailability of data. However, this large-scale population-based study with a long duration period provided real-world data without selection bias.

Conclusion

In patients with SCLC, a diagnosis of COPD was associated with reduced 1-year mortality, but no significant difference after 1-year. Age, BMI, and some comorbidities, such as CHF and diabetes, play an important role in survival. After the diagnosis of SCLC, clinicians should actively screen for coexisting comorbidities because early detection and treatment may improve outcomes in those patients.

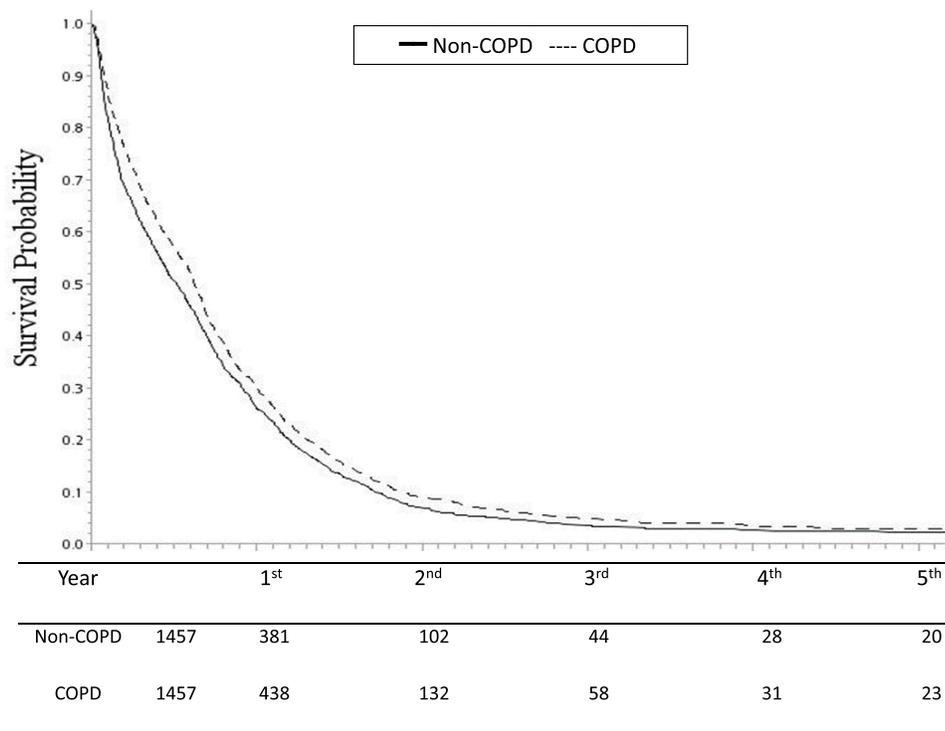


Figure 2 Survival probability of COPD and non-COPD cohorts.

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Disclosure

The authors report no conflicts of interest in this work.

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