ORIGINAL RESEARCH

Impact of Smoking and Chronic Obstructive Pulmonary Disease on All-Cause, Respiratory, and Cardio-Cerebrovascular Mortality

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Introduction: Mortality differences in chronic obstructive pulmonary disease (COPD) between nonsmokers and smokers remain unclear. We compared the risk of death associated with smoking and COPD on mortality.

Methods: The study included participants aged ≥40 years who visited pulmonary clinics and were categorised into COPD or non-COPD and smoker or nonsmoker on the basis of spirometry results and cigarette consumption. Mortality rates were compared between groups using statistical analysis for all-cause mortality, respiratory disease-related mortality, and cardiocerebrovascular disease-related mortality.

Results: Among 5811 participants, smokers with COPD had a higher risk of all-cause (adjusted hazard ratio (aHR), 1.69; 95% confidence interval (CI), 1.23–2.33) and respiratory disease-related mortality (aHR, 2.14; 95% CI, 1.20–3.79) than nonsmokers with COPD. Non-smokers with and without COPD had comparable risks of all-cause mortality (aHR, 1.39; 95% CI, 0.98–1.97) and respiratory disease-related mortality (aHR, 1.77; 95% CI, 0.85–3.68). However, nonsmokers with COPD had a higher risk of cardiocerebrovascular disease-related mortality than nonsmokers without COPD (aHR, 2.25; 95% CI, 1.15–4.40).

Conclusion: The study found that smokers with COPD had higher risks of all-cause mortality and respiratory disease-related mortality compared to nonsmokers with and without COPD. Meanwhile, nonsmokers with COPD showed comparable risks of all-cause and respiratory mortality but had a higher risk of cardiocerebrovascular disease-related mortality compared to nonsmokers without COPD.

Keywords: pulmonary disease, chronic obstructive, smokers, nonsmokers, cigarette smoking, comorbidity

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally.[1] COPD is persistent airflow limitation and lung tissue damage due to prolonged environmental factor exposure in individuals with a genetic predisposition.[2] Effective inhaled therapy has long been developed for COPD management.[3] Recently, inhaled triple pharmacologic therapy, combining inhaled corticosteroids (ICS), long-acting muscarinic antagonists (LAMA), and long-acting β2-agonists (LABA), has showed treatment effectiveness in severe COPD.[4] The most significant risk factor for the development of COPD is smoking. However, other factors, such as exposure to air pollutants or workplace fumes and dust, genetic factors, and repeated lower airway infections, can also cause COPD, which has been reported in nonsmokers.[5,6] Nonsmokers account for 25–45% of all patients with COPD. Studies have shown that COPD in nonsmokers displays different clinical features than that in smokers.[5,7–12] This distinction is further endorsed in GOLD 2023 which classifies COPD types in nonsmokers as different from COPD in smokers.[3] However, so far, large

COPD cohort studies and trials have systematically excluded nonsmokers; therefore, the clinical characteristics and outcomes, including mortality risk in nonsmokers with COPD, have not been fully investigated.[13] A few studies[14–16] have compared mortality risk between smokers with COPD and nonsmokers with COPD. However, these studies have limitations, such as a lack of postbronchodilator spirometry results,[14,15] insufficient adjustment for covariates,[14] and a low number of participants.[16]

Studies have reported that nonsmokers with COPD have a milder clinical course and airflow limitation compared with smokers with COPD.[17–19] Therefore, we hypothesized that nonsmokers with COPD show a different mortality risk compared with smokers with COPD. The aim of the present study was to compare the risk of all-cause mortality, respiratory disease-related mortality, and cardiocerebrovascular disease-related mortality risks between smokers with COPD and nonsmokers with COPD using an observational cohort. Additionally, we analyzed non-smokers with COPD and non-smokers without COPD to determine the effect of COPD on mortality.

Methods

Study Design and Population

This retrospective observational study was conducted at Seoul National University Hospital, a tertiary care service center. We included patients aged ≥ 40 years who visited the pulmonology outpatient clinic between September 21st, 2009 and December 31st, 2015. Patients who underwent postbronchodilator spirometry tests to evaluate their airway obstruction state were included. Patients with a history of any cancer, diagnosed with diffuse interstitial lung disease, bronchiectasis, tuberculosis-destroyed lung, or a lack of smoking data were excluded from this study. We defined COPD as a postbronchodilator forced expiratory volume in 1 second (FEV1)/vital capacity of < 0.7. Participants who smoked at least 100 cigarettes in their lifetime were categorized as smokers, whereas those who smoked fewer than 100 cigarettes were classified as never-smokers.[20] However, for the purpose of comparison grouping, we defined smokers as participants with ≥10 pack-years of cumulative cigarette consumption and nonsmokers as participants <10 pack-years of cumulative cigarette consumption. This classification aligns with previous trends in COPD research[21–24] Participants were categorized into four groups: smokers with COPD, nonsmokers with COPD, smokers without COPD, and nonsmokers without COPD.

Variables and Definitions

Medical records were used to review the patients' baseline characteristics, including age, sex, and body mass index (BMI). Past medical history and comorbidities were determined for each patient using diagnosed International Classification of Diseases (ICD)-10 codes as follows: C0–C9, any cancer; E10–E14, diabetes mellitus; I10–I15, hypertension; I20–I25, coronary artery disease; I60–I69, cerebral vascular disease; and I50, heart failure. In addition, smoking history, including pack-years, was reviewed. Spirometry was measured by qualified technicians using the standardized spirometry method of the European Respiratory Society.[25] Appropriate testing was performed in triplicate using a valid and reproducible effort spirometry method.[26,27] Postbronchodilator spirometry was measured 10–20 min after inhaling 400 µg of salbutamol administered as a metered-dose inhaler to the patient.[28] Results of the postbronchodilator spirometry testing were obtained as FEV1 L/s, where FEV1 was expressed as a percentage of predicted values (FEV1%). The index date was defined as the first date of postbronchodilator spirometry during the enrollment period.

Treatment, including inhaled corticosteroid, long-acting β_2-agonist, and long-acting muscarinic antagonist, during follow-up was also evaluated. Some patients were treated with multiple combinations of inhaled drugs. We conducted an assessment of medical records from August 12, 2020 to February 28, 2021.

As of December 31st, 2019, the mortality data of all patients were investigated from the Statistics Korea database (http://kostat.go.kr/portal/eng/index.action). The date and cause of death were acquired from the Statistics Korea database. The specific cause of death was confirmed by the Statistics Korea database and stated as an ICD code as follows: ICD J00–J99, respiratory disease-caused death and ICD I00–I99, cardiocerebrovascular disease-related death.

The primary outcome was all-cause mortality and the secondary outcomes were respiratory disease-caused mortality and cardiocerebrovascular disease-related mortality.

Statistical Analyses

Differences in characteristics between groups were compared using Chi-square test for categorical variables and the analysis of variance for continuous variables. Mortality risks were analyzed by Kaplan–Meier estimates, multivariable cox proportional hazard regression models adjusted by confounders with hazard ratio (aHR), and 95% confidence intervals (CIs). In the main analysis, we compared four groups (smokers with COPD, nonsmokers with COPD, smokers without COPD, and nonsmokers without COPD) and also analyzed the participants according to categorization into six groups (never smokers with COPD, <10 pack-year smokers with COPD, ≥10 pack-year smokers with COPD, never smokers without COPD, <10 pack-year smokers without COPD, and ≥10 pack-year smokers without COPD). *P*-values < 0.05 were considered statistically significant. All analyses were performed using Stata 17.0 (Stata Corp, College Station, Texas, USA).

We confirm that all methods were carried out in accordance with relevant guidelines and regulations. The present study was approved by the institutional review boards of Seoul National University Hospital (IRB no. H-2008-053-1147) and the requirement for patients' informed consent was waived. This waiver was granted because the study involved minimal risk to participants and utilized anonymized data. Patient data confidentiality was strictly maintained, and all procedures were in compliance with the Declaration of Helsinki.

Results

Baseline Characteristics of the Study Population

During the study period, 25,787 patients visited pulmonology clinics and underwent postbronchodilator spirometry testing. Among these patients, 10,924 with any cancer, 1072 with diffuse interstitial lung disease, 1605 with bronchiectasis, and 92 patients with tuberculosis-destroyed lung were excluded from the study. A further 6283 patients who lacked information about smoking history were also excluded. A final total of 5811 patients were eligible for our study. Participants were classified as COPD (2256 patients, 38.8%) and non-COPD (3555 participants, 61.2%) groups. Patients were also classified according to smoking status as follows: 1228 (21.1%) patients were classified as smokers with COPD; 1028 (17.7%) patients were nonsmokers with COPD; 920 (15.8%) were smokers without COPD, and 2635 (45.3%) were nonsmokers without COPD (Figure 1).
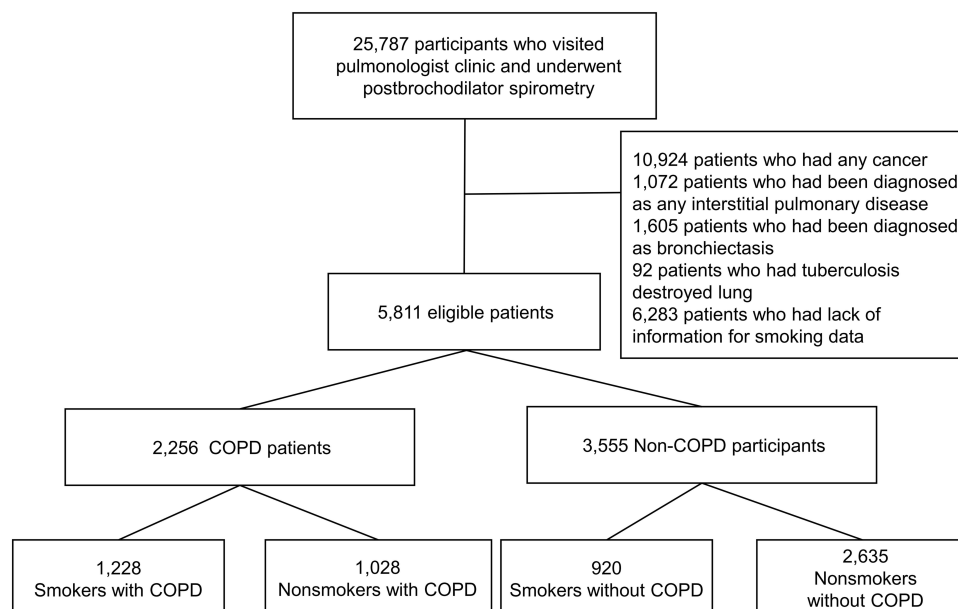

Figure 1 Flow chart of inclusion and categorization of study participants. Postbronchodilator spirometry includes the pre- and post-bronchodilator forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and the ratio of these values (FEV1/FVC).
Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 1 Baseline Characteristics of the Study Participants

Variables	COPD (n = 2256)		Non-COPD (n = 3555)		P-value
	Smokers (n = 1228)	Nonsmokers (n = 1028)	Smokers (n = 920)	Nonsmokers (n = 2635)	
Age, mean ± SD	67.8 ± 9.4	67.9 ± 10.3	60.1 ± 10.6	60.9 ± 10.5	<0.001
Male, n (%)	1183 (96.3)	423 (41.2)	854 (92.8)	503 (19.1)	<0.001
BMI, mean ± SD	23.3 ± 3.5	23.6 ±3.5	24.4 ± 15.4	24.5 ± 8.7	<0.001
Smoking history					<0.001
Current smoker, n (%)	498 (40.6)	0 (0.0)	362 (39.4)	0 (0.0)	
Former smoker, n (%)	730 (59.5)	0 (0.0)	558 (60.7)	0 (0.0)	
Never smoker, n (%)	0 (0.0)	1028 (100.0)	0 (0.0)	2635 (100.0)	
Pack-years, mean ± SD	41.6 ± 22.3	0.0	31.7 ± 19.1	0.0	<0.001*
History of TB, n (%)	24 (2.0)	33 (3.2)	20 (2.2)	43 (1.6)	0.026
Diabetes mellitus, n (%)	135 (11.0)	103 (10.0)	127 (13.8)	219 (8.3)	<0.001
Hypertension, n (%)	176 (14.3)	173 (16.8)	101 (11.0)	250 (9.5)	<0.001
Dyslipidemia n, (%)	123 (10.0)	92 (9.0)	44 (4.8)	106 (4.0)	<0.001
Coronary artery disease n, (%)	229 (18.7)	127 (12.4)	134 (14.6)	255 (9.7)	<0.001
Heart failure, n (%)	40 (3.3)	59 (5.7)	25 (2.7)	68 (2.6)	<0.001
Cerebrovascular disease,n (%)	122 (9.9)	102 (9.9)	133 (14.5)	276 (10.5)	0.002

Note: *Comparison of smokers with COPD vs smokers without COPD.
Abbreviations: COPD, chronic obstructive pulmonary disease; SD, standard deviation; BMI, body mass index; TB, tuberculosis.

The baseline characteristics of the patients included in the study are shown in Table 1 and Supplemental Table 1. Smokers were predominantly male in both the COPD (96.3%) and non-COPD (92.8%) groups, whereas nonsmokers were mainly female in both the COPD (58.8%) and non-COPD (80.9%) groups. Patients with COPD had a greater cigarette consumption than those without COPD (41.6 ± 22.3 vs 31.7 ± 19.1 pack-years; $P < 0.001$). All four groups showed statistically significant differences in the prevalence of comorbidities, and smokers with COPD had the highest proportion of coronary artery disease (18.7%), followed by smokers without COPD (14.6%), nonsmokers with COPD (12.4%), and nonsmokers without COPD (9.7%).

Postbronchodilator FEV1 values were comparable between smokers and nonsmokers with COPD. Half of the patients were categorized as Global Initiative for Chronic Obstructive Lung Disease grade 1 (FEV1 ≥ 80% of predicted value) in both groups (Table 2). Inhaled treatments for patients with COPD are described in Table 2.

Mortality Risk

A total of 449 deaths occurred during a median of 6.2 years of follow-up. The causes of death are described in Supplemental Table 2. The estimated 5-year mortality rates of smokers with COPD, nonsmokers with COPD, smokers without COPD, and nonsmokers without COPD were 12.5%, 8.1%, 5.6%, and 2.3%, respectively. The estimated 5-year respiratory disease-related mortality rates of smokers with COPD, nonsmokers with COPD, smokers without COPD, and nonsmokers without COPD were 5.2%, 2.6%, 1.6%, and 0.4%, respectively. The estimated 5-year cardiocerebrovascular disease-related mortality rates of smokers with COPD, nonsmokers with COPD, smokers without COPD, and non-smokers without COPD were 2.7%, 2.2%, 0.9%, and 0.4%, respectively. Crude mortality without adjustment revealed

Table 2 Baseline Pulmonary Function and Inhaled Treatment in Patients with COPD

Variables	Smokers with COPD (n = 1228)	Nonsmokers with COPD (n = 1028)	*P*-value
GOLD grade			0.073
FEV1 ≥ 80% of predicted	618 (50.3)	528 (51.4)	
50 ≤ FEV1 < 80% of predicted value	452 (36.8)	385 (37.5)	
30 ≤ FEV1 < 50% of predicted value	130 (10.6)	106 (10.3)	
FEV1<30% of predicted value	28 (2.3)	9 (0.9)	
FEV1, L	1.87 ± 0.68	1.83 ± 0.67	0.121
FEV1, % of predicted value, mean ± SD	77.8 ± 23.1	79.1 ± 22.7	0.174
FEV1/FVC, mean ± SD	55.73 ± 12.1	57.4 ± 10.8	<0.001
Inhaled treatments, n (%)			
ICS	509 (41.5)	542 (54.7)	<0.001
LABA	316 (25.7)	183 (17.8)	<0.001
LAMA	618 (50.3)	341 (33.2)	<0.001
No regular inhaled treatment	416 (33.9)	381 (37.1)	0.115

Note: FEV1 and FVC values are postbronchodilator.
Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Obstructive Lung Disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; LABA, long-acting β2 agonists; LAMA, long active muscarinic antagonist; ICS, inhaled corticosteroid.

that smokers with COPD showed the highest all-cause and respiratory disease-related mortality (*P* < 0.001 and *P* < 0.001, respectively) (Figure 2, Supplemental Table 3).

After adjustment for age, sex, BMI, and comorbidities (history of tuberculosis, diabetes mellitus, coronary artery disease, heart failure, cerebrovascular disease), smokers with COPD had a higher risk of all-cause mortality (aHR, 2.36; 95% CI, 1.60–3.48), respiratory-related mortality (aHR, 3.46; 95% CI, 1.60–7.49), and cardiocerebrovascular disease-related mortality (aHR, 2.88; 95% CI, 1.31–6.32) than nonsmokers without COPD. Smokers with COPD had a higher risk of all-cause mortality (aHR, 1.69; 95% CI, 1.23–2.33), and respiratory-related mortality (aHR, 2.14; 95% CI, 1.20–3.79) than nonsmokers with COPD, whereas risk of cardiocerebrovascular disease-related mortality (aHR, 1.28; 95% CI, 0.70–2.32) was comparable to that of nonsmokers with COPD. Nonsmokers with COPD had a higher risk of cardiocerebrovascular disease-related mortality (aHR, 2.25; 95% CI, 1.15–4.40) than nonsmokers without COPD, although there were no differences in risks of all-cause mortality (aHR, 1.39; 95% CI, 0.98–1.97) and respiratory-related mortality (aHR, 1.77; 95% CI, 0.85–3.68) between the two groups. Smokers without COPD had a higher risk of all-cause mortality (aHR, 1.48; 95% CI, 1.01–2.17) than nonsmokers with COPD, whereas there were no differences in risks of respiratory-related mortality (aHR, 1.45; 95% CI, 0.70–2.99) and cardiocerebrovascular disease-related mortality (aHR, 1.02; 95% CI, 0.49–2.12) between the two groups (Figure 2).

Analysis of Participants by Categorization into Six Groups

Smokers with a ≥10 pack-year history with COPD had a higher risk of all-cause mortality (aHR, 2.35; 95% CI, 1.58–3.49), respiratory disease-related mortality (aHR, 3.61; 95% CI, 1.65–7.90), and cardiocerebrovascular disease-related mortality (aHR, 2.68; 95% CI, 1.21–5.92) than never smokers without COPD. However, smokers with <10 pack-years with COPD and never smokers without COPD had comparable risks of all-cause mortality (aHR, 1.34; 95% CI, 0.41–4.34) and respiratory disease-related mortality (aHR, 1.89; 95% CI, 0.24–15.1). Never smokers with COPD had a similar

(a) All-cause mortality
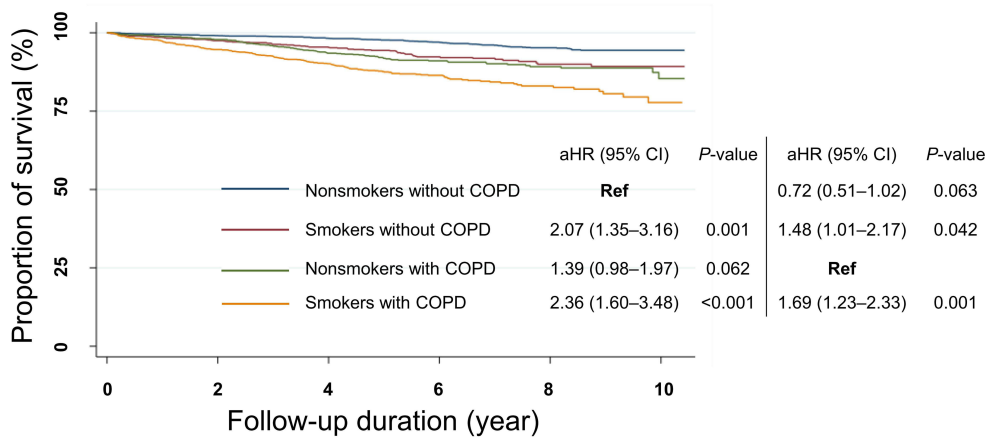
(b) Respiratory disease-related mortality
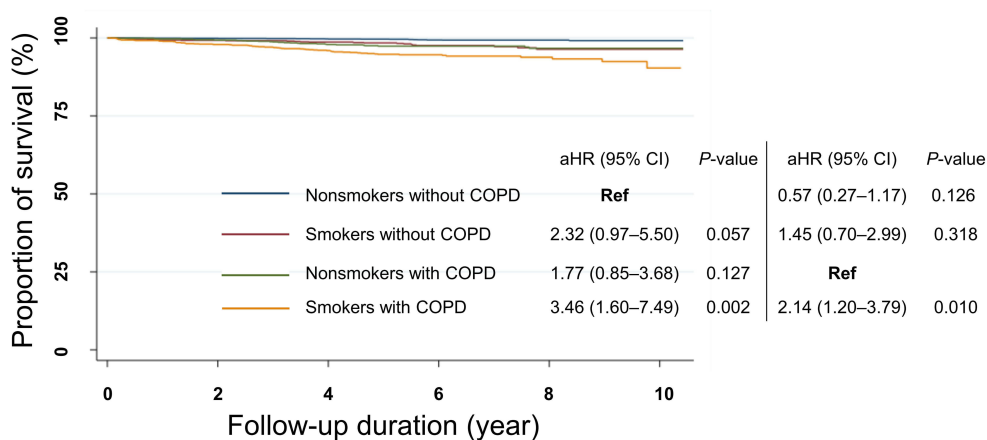
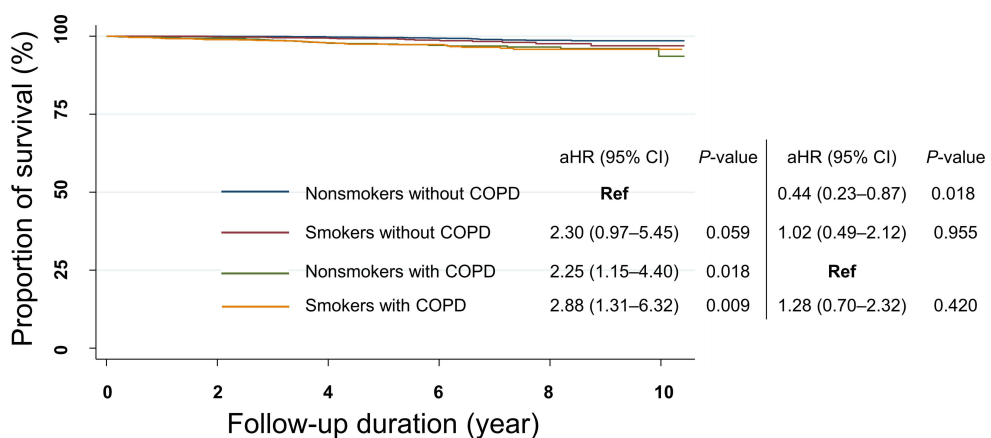**(c) Cardio-cerebrovascular disease-related mortality**

Figure 2 Comparison of mortality risks between the groups. (**a**) All-cause mortality; (**b**) respiratory disease-related mortality; (**c**) cardiocerebrovascular disease-related mortality adjusted for age, sex, body mass index, and comorbidities (hypertension, dyslipidemia, coronary artery disease, cerebrovascular disease, heart failure, diabetes mellitus, history of tuberculosis).
Abbreviations: aHR, adjusted hazard ratio; COPD, chronic obstructive pulmonary disease.

Table 3 Mortality Risk After Categorization of Participants into Never Smokers, <10 Pack-Year Smokers, and ≥10 Pack-Year Smokers

Group		All-Cause Mortality		Respiratory Disease-Related Mortality		Cardio-Cerebrovascular Disease-Related Mortality	
		aHR* (95% CI)	P-value	aHR* (95% CI)	P-value	aHR* (95% CI)	P-value
Non-COPD participants	Never smokers	Ref		Ref		Ref	
	<10 PY smokers	0.93 (0.22–3.85)	0.919	0 (0.00–0.00)	1.000	0 (0.00–0.00)	1.000
	≥10 PY smokers	2.06 (1.33–3.17)	0.001	2.45 (1.02–5.88)	0.045	2.14 (0.90–5.09)	0.087
Patients with COPD	Never smokers	1.39 (0.98–1.98)	0.068	1.70 (0.82–3.54)	0.156	2.25 (1.15–4.40)	0.018
	<10 PY smokers	1.34 (0.41–4.34)	0.627	1.89 (0.24–15.1)	0.549	0 (0.00–0.00)	1.000
	≥10 PY Smokers	2.35 (1.58–3.49)	<0.001	3.61 (1.65–7.90)	0.001	2.68 (1.21–5.92)	0.015

Notes: *Adjusted for age, sex, body mass index, and comorbidities (hypertension, dyslipidemia, coronary artery disease, cerebrovascular disease, heart failure, diabetes mellitus, and history of tuberculosis).
Abbreviations: COPD, chronic obstructive pulmonary disease; aHR, adjusted hazard ratio; PY, pack-year.

risk of all-cause mortality (aHR, 1.39; 95% CI, 0.98–1.98) and respiratory disease-related mortality (aHR, 1.70; 95% CI 0.82–3.54) but a higher risk of cardiocerebrovascular disease-related mortality (aHR, 2.25; 95% CI 1.15–4.40) than never smokers without COPD (Table 3).

In patients with COPD, after additional adjustment for inhaled medication, smokers with ≥10 pack-years had a higher risk of all-cause mortality (aHR, 1.85; 95% CI, 1.30–2.65) and respiratory disease-related mortality (aHR, 2.20; 95% CI, 1.19–4.09) than never smokers with COPD. However, smokers with <10 pack-years and never smokers with COPD had comparable risks of all-cause mortality (aHR, 0.90; 95% CI, 0.28–2.91) and respiratory disease-related mortality (aHR, 1.00; 95% CI, 0.13–7.68) (Supplemental Table 4).

In participants without COPD, smokers with ≥10 pack-years had a higher risk of all-cause mortality (aHR, 2.06; 95% CI, 1.33–3.17) and respiratory disease-related mortality (aHR, 2.45; 95% CI 1.02–5.88) than never smokers without COPD but a comparable risk of cardiocerebrovascular disease-related mortality (aHR, 2.14; 95% CI, 0.90–5.09). Smokers with <10 pack-years smoking history and never smokers without COPD showed a comparable risk of all-cause mortality (aHR, 0.93; 95% CI, 0.22–3.85) (Table 3).

Discussion

The present observational cohort study, which included 5811 participants, investigated the impact of smoking history on mortality risk in patients with COPD. Smokers with COPD showed significantly higher risks of all-cause and respiratory disease-related mortality than nonsmokers with COPD. Nonsmokers with COPD had a comparable all-cause and respiratory disease-related mortality risk but higher cardiocerebrovascular disease-related mortality risk than nonsmokers without COPD. Smokers with <10 pack-years of cumulative cigarette consumption showed no significant differences in all-cause mortality risk compared with never smokers in both COPD and non-COPD groups.

While only a few studies have compared mortality risk between never smokers with COPD and smokers with COPD, these have shown conflicting results.[14–16] Shavelle et al analyzed the US third National Health and Nutrition Examination Survey and found a higher reduction in life-expectancy in current smokers with COPD than never smokers with COPD.[15] However, one limitation of their study was that COPD diagnosis was based on prebronchodilator spirometry at a mobile examination center or portable spirometer in the home. The guidelines recommend postbronchodilator spirometry to determine a persistent airflow limitation[3,29] and our study defined patients with COPD thoroughly using postbronchodilator spirometry results. Thomsen et al conducted a population-based observational study in Denmark and found that former and current smokers with COPD had a higher risk of all-cause mortality than never smokers without COPD, whereas there were no significant differences in risk of all-cause mortality between never smokers with COPD and never smokers without COPD.[14] They studied a broad aspect of COPD-related outcomes and applied prebronchodilator

spirometry results and excluded smokers without COPD. Unfortunately, their results of mortality risk were only adjusted for age and sex. Tobacco smoking is associated with COPD and many other comorbidities, such as cardiovascular disease or cancer.[30] These comorbidities could have confounding effects on mortality risk in people with COPD. Therefore, we included smokers without COPD to exclude the confounding effects of smoking on mortality and adjusted for various confounders, including age, sex, BMI, and significant comorbidities, such as diabetes mellitus, hypertension, coronary artery disease, heart failure, and cerebrovascular disease.

Ramírez-Venegas et al studied survival in 520 patients with COPD, including never smokers with COPD who cooked with a biomass stove compared with tobacco smokers with COPD.[16] They showed that there were no significant differences in all-cause mortality between tobacco smokers with COPD and patients with COPD inhaling biomass smoke after adjustment for lung function, BMI, age, and oxygen saturation. Unfortunately, in the present study, the causes of COPD in nonsmokers were unknown, but the cooking stoves currently used in Korea are gas or electric and there is a low possibility that our cohort included patients with COPD who cooked using biomass stoves. Therefore, we assumed that the nonsmokers in our cohort had different risk factors than those in the study reported by Ramírez-Venegas et al and the different risk factors of COPD and survival outcomes in nonsmokers between our study and theirs suggest that specific mortality risks could differ according to specific causes or risk factors in never smokers with COPD.

Our results indicated that smokers with COPD demonstrated a higher risk of mortality than nonsmokers with COPD. Intriguingly, nonsmokers with COPD exhibited a comparable risk of all-cause and respiratory disease-related mortality compared with nonsmokers without COPD. These results are congruent with those reported by Thomsen et al, who revealed that never-smokers with COPD demonstrated a comparable risk of all-cause mortality compared with never-smokers without COPD. Previous research has revealed the detrimental effects of smoking. Cigarette smoke induces oxidative stress, inflammation, and cellular senescence throughout various organ systems at the fundamental science level.[31,32] Furthermore, Pezzuto et al indicate that even one month of short-term smoking cessation improved lung function and cholesterol levels, which corroborates our results of smokers exhibiting worse survival on respiratory or cardiovascular disease.[33] Furthermore, we revealed that nonsmokers with COPD demonstrated a lower risk of all-cause mortality than smokers without COPD. Smoking itself exhibits a significant impact on mortality,[34] thus, smokers without COPD had a higher risk than nonsmokers with COPD.

Smokers without COPD demonstrated a mortality risk similar to that of smokers with COPD. This group was younger and reported a lower average smoking amount (measured in pack-years) compared to smokers with COPD. We hypothesize that smokers without COPD may remain at risk of developing COPD, or they may possess a slower nicotine metabolism or different gene expressions, affecting their potential for developing COPD.[35,36]

Cardiovascular diseases are prevalent comorbidities in patients with COPD and previous studies revealed that COPD could increase the risk of myocardial infarction or stroke and COPD was attributed to poor cardiovascular disease outcomes[37–40] The association between COPD and cardiovascular disease is well-established. However, the increased risk of cardiovascular disease by COPD, or smoking as a confounding factor, remains unclear. Our study revealed that nonsmokers with COPD demonstrated a higher risk of cardiocerebrovascular disease-related mortality than nonsmokers without COPD. This indicates that COPD poses a significant risk of cardiocerebrovascular disease-related death despite eliminating the risk factor of smoking. Furthermore, previous studies revealed that a decline in FEV1 in nonsmokers with COPD is associated with an increased risk of cardiovascular death.[41] Additionally, intermittent hypoxia in patients with COPD induced proinflammatory cytokines and oxidative stress, thereby increasing the risk of atherosclerosis and vascular remodeling.[42,43] We previously reported that biomass-exposed nonsmokers with COPD demonstrated a similar risk of COPD exacerbation compared with smokers with COPD.[44]

The results of our study exhibit the following clinical implications. First, smoking cause early excessive mortality in patients with COPD. The risk of all-cause mortality among smokers is higher than that among never smokers.[45,46] The leading causes of death in smokers are malignancies (including lung cancer), cardiocerebrovascular diseases, and respiratory diseases.[30,46] Our study excluded patients with cancer, but smokers with COPD demonstrated higher risks of all-cause mortality and respiratory mortality than nonsmokers with COPD, and the most predominant cause of death was related to respiratory disease (Supplemental Table 2). Smokers are susceptible to respiratory infection, and smoking is a known risk factor for acute exacerbation of COPD,[47,48] which causes a higher risk of mortality in smokers with

COPD than nonsmokers with COPD. COPD per se generally causes early excessive mortality.[49–51] However, our study revealed that nonsmokers with COPD exhibited a lower risk of all-cause mortality than smokers without COPD after adjustment for age, sex, BMI, and comorbidities (Figure 2A). A previous study also revealed that COPD per se did not affect the risk of mortality which was affected by smoking status and comorbidities, particularly in patients with COPD with mild-to-moderately impaired FEV1.[52] These results indicate that early excessive mortality is affected by smoking and smoking-related comorbidities rather than COPD.

Second, data from non-smokers indicate that COPD alone significantly increases the risk of cardiocerebrovascular diseases-related death. This result emphasizes the independent impact of COPD on cardiovascular health, regardless of traditional risk factors such as smoking. It indicates that the COPD-associated inflammatory processes may contribute to cardiovascular and cerebrovascular complications, causing a higher mortality rate. This connection emphasizes the need for comprehensive cardiovascular monitoring and preventive strategies in patients with COPD, regardless of their smoking status.

Third, nonsmokers and smokers with COPD have different phenotypes. Previous studies showed differences in the clinical and radiological features between smokers and nonsmokers with COPD.[11,14,17,19] Nonsmokers with COPD had diseases limited to the lungs and showed low systemic inflammation or were not at increased risk of extrapulmonary complications. However, smokers with COPD showed more systemic inflammation and extrapulmonary complications.[13,14] The clinical features of symptoms and airway limitations were milder in nonsmokers than smokers.[17] Furthermore, imaging revealed that nonsmokers with COPD showed an airway predominant subtype, whereas smokers with COPD showed emphysema predominant phenotypes.[11] In the present study, even after excluding deaths from lung cancer or other cancers, which are well-known smoking-related causes of death,[52,53] all-cause mortality and respiratory disease-related mortality were higher in smokers with COPD than nonsmokers with COPD. Taken together, the results from previous studies and our results show different risks in mortality between smokers and nonsmokers with COPD, that smokers and nonsmokers with COPD may be considered to have different phenotypes.

Our study defined smokers as those with ≥10 pack-years of cumulative cigarette consumption, as previously adopted by many studies.[54–56] However, the cutoff point of "smokers" was not based on sufficient scientific evidence. In our study, never smokers (0 pack-years) and smokers with <10 pack-years showed a comparable risk of mortality, whereas smokers with ≥10 pack-years showed a significantly higher risk of mortality, which did not depend on the presence or absence of COPD. Thus, our results support defining smokers according to a cutoff point of 10 pack-years of cumulative cigarette consumption.

Conclusion

Our observational study revealed that smokers with COPD demonstrated higher risks of all-cause mortality and respiratory disease-related mortality than nonsmokers with COPD and nonsmokers without COPD. Nonsmokers with COPD exhibited comparable risks of all-cause and respiratory mortality but a risk of higher cardiocerebrovascular disease-related mortality than nonsmokers without COPD. The results of the present study indicate that physicians need to recognize that the disease course of COPD varies between smokers and nonsmokers.

Abbreviations

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FEV1%, FEV1 expressed as percentage of predicted values; ICD, International Classification of Diseases.

Data Sharing Statement

Data supporting the findings of this study are available from the corresponding author upon request.

Statement of Ethics

We confirm that all methods were carried out in accordance with relevant guidelines and regulations. The present study was approved by the institutional review boards of Seoul National University Hospital (IRB no. H-2008-053-1147) and the requirement for patients' informed consent was waived.

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Disclosure

The authors report no conflicts of interest in this work.

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