ORIGINAL ARTICLE
https://doi.org/10.4046/trd.2021.0121
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2022;85:74-79

Chronic Obstructive Pulmonary Disease Is Not Associated with a Poor Prognosis in COVID-19

Youlim Kim, M.D.[1,2,*], Tai Joon An, M.D.[3,*], Yong Bum Park, M.D.[4], Kyungjoo Kim, M.Sc.[5], Do Yeon Cho[6], Chin Kook Rhee, M.D., Ph.D.[5] and Kwang-Ha Yoo, M.D., Ph.D.[1]

[1]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Konkuk University Hospital, Konkuk University School of Medicine, Seoul, [2]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Chuncheon Sacred Heart Hospital, Chuncheon, [3]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [4]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, [5]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, [6]Big Data Research Division, Health Insurance Review and Assessment Service, Wonju, Republic of Korea

Background: The effect of underlying chronic obstructive pulmonary disease (COPD) on coronavirus disease 2019 (COVID-19) during a pandemic is controversial. The purpose of this study was to examine the prognosis of COVID-19 according to the underlying COPD.

Methods: COVID-19 patients were assessed using nationwide health insurance data. Comorbidities were evaluated using the modified Charlson Comorbidity Index (mCCI) which excluded COPD from conventional CCI scores. Baseline characteristics were assessed. Univariable and multiple logistic and linear regression analyses were performed to determine effects of variables on clinical outcomes. Ages, sex, mCCI, socioeconomic status, and underlying COPD were selected as variables.

Results: COPD patients showed older age (71.3±11.6 years vs. 47.7±19.1 years, p<0.001), higher mCCI (2.6±1.9 vs. 0.8±1.3, p<0.001), and higher mortality (22.9% vs. 3.2%, p<0.001) than non-COPD patients. The intensive care unit admission rate and hospital length of stay were not significantly different between the two groups. All variables were associated with mortality in univariate analysis. However, underlying COPD was not associated with mortality unlike other variables in the adjusted analysis. Older age (odds ratio [OR], 1.12; 95% confidence interval [CI], 1.11–1.14; p<0.001), male sex (OR, 2.29; 95% CI, 1.67–3.12; p<0.001), higher mCCI (OR, 1.30; 95% CI, 1.20–1.41; p<0.001), and medical aid insurance (OR, 1.55; 95% CI, 1.03–2.32; p=0.035) were associated with mortality.

Conclusion: Underlying COPD is not associated with a poor prognosis of COVID-19.

Keywords: COVID-19; Chronic Obstructive Pulmonary Disease; Prognosis

Address for correspondence: Kwang-Ha Yoo, M.D., Ph.D.
Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Konkuk University Hospital, Konkuk University School of Medicine, 120 Neungdong-ro, Gwangjin-gu, Seoul 05030, Republic of Korea
Phone: 82-2-2030-7014, **Fax:** 82-2-2030-7018, **E-mail:** khyou@kuh.ac.kr
*Youlim Kim and Tai Joon An contributed equally to this work.
Received: Aug. 3, 2021, **Revised:** Sep. 7, 2021, **Accepted:** Oct. 15, 2021, **Published online:** Nov. 11, 2021

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2. It mainly enters the lung as its target[1]. Therefore, patients with chronic pulmonary disease such as chronic obstructive pulmonary disease (COPD) are worried about COVID-19. Several articles have reported the prevalence and outcomes of COPD patients with COVID-19[2,3]. However, prevalence and results showed variabilities due to limitations of current studies[2,3]. Thus, effects of underlying COPD on prevalence and outcomes of COVID-19 remain controversial[4]. South Korea has a nationwide medical claims database for almost all medical information, including medication use. Thus, the objective of this study was to analyze the effects of COPD on COVID-19 using this well-established database.

Materials and Methods

1. Data sources

South Korea a single mandatory government health insurance system. The Health Insurance Review and Assessment Service (HIRA) is responsible for evaluating data of medical claims in South Korea. Almost all South Koreans are included in this system[5]. We retrospectively analyzed data from the HIRA database. To promote real-world COVID-19 research, HIRA provides claims data for confirmed COVID-19 cases to the public, including confirmed cases up to May 15, 2020. To analyze comorbidities and effects of medications, we examined the data from January 20, 2019, one year before the first confirmed case, to May 15, 2020.

2. Study population

Confirmed COVID-19 cases were defined as individuals with a confirmed infection based on diagnostic testing standards such as a COVID-19 nucleic acid testing (real-time polymerase chain reaction) recommended by the Korean Disease Control and Prevention Agency (KDCA). Nasopharyngeal and oropharyngeal swabs were required for the confirmation. Sputum specimens were also collected if patients had sputum.

All COVID-19 patients in South Korea are managed by the KDCA. They were all isolated at hospitals or in residential treatment centers after COVID-19 was confirmed. They were released from isolation after showing no clinical symptom for 10 days upon confirmation with negative results of polymerase chain reaction tests twice in a row (at least a 24-hour interval) after 7 days upon confirmation. The list of all patients was managed and merged with HIRA claims data by the KDCA. The KDCA also provides mortality outcomes due to COVID-19 to HIRA. Patients were enrolled if they had confirmed COVID-19 or had died from COVID-19 with age of at least 18 years and medical claims data obtained in the year before the date of COVID-19 diagnosis. Patients were excluded if they were younger than 18 years, had no linked medical claims data for confirmed or deceased cases, or had no medical claims data for the year from the date of COVID-19 diagnosis.

3. Operational definition of COPD

The operational definition of patients with COPD was as follows: (1) age ≥40 years, (2) at least one International Classification of Disease, 10th revision (ICD-10) diagnosis code for COPD or emphysema (J43.0x–J44.x, except J43.0 as a primary or secondary [within four positions] diagnosis), and (3) the use of more than one of the following COPD medications at least twice per year: long-acting muscarinic antagonist (LAMA), long-acting β_2 agonist (LABA), inhaled corticosteroid plus LABA (ICS+LABA), LABA+LAMA, short-acting muscarinic antagonist (SAMA), short-acting β_2 agonist (SABA), SAMA+SABA, phosphodiesterase-4 inhibitor, methylxanthine, and oral beta-adrenergic agonist[6-11].

4. Comorbidities

Modified Charlson Comorbidity Index (mCCI) was used to predict prognosis and mortality. Conventional CCI was based on ICD-10 diagnosis code and mCCI excluded the factor of COPD diagnosis from conventional CCI (Supplementary Table S1)[12].

5. Management of COVID-19 in this study

This study was performed with data until May 15, 2020. Until then, management of COVID-19 was mainly symptomatic treatment. Other drugs such as Remdesivir and dexamethasone were not used as treatment for COVID-19 of participants in this study.

6. Ethics approval

All methods of this study were carried out in accordance with relevant guidelines and regulations. This study was approved by the Institutional Review Board of The Catholic University of Korea Yeouido St. Mary's Hospital (approval no. SC20ZISE0067). Informed consent was waived due to the retrospective nature of this study.

7. Statistical analyses

Student's t-test and chi-square test for independence were used to compare differences in continuous and categorical

variables between groups. Simple and multiple linear regression analyses were performed to find factors affecting hospital length of stay (LOS). Univariable and multiple logistic regression analyses were used to find factors affecting admission to an intensive care unit (ICU) and mortality. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

1. Demographics of COVID-19 patients in South Korea

Of 11,018 confirmed cases of COVID-19 during the study period, there were 7,590 matched cases with medical claims data in the HIRA. After excluding young subjects (<40 years old) and those lacking medical claims data, 6,520 subjects were included finally. Of these patients, we classified the COPD group using the operational definition of COPD: (1) age ≥40 years, (2) at least one ICD-10 diagnosis code for COPD or emphysema (J43.0x–J44.x, except J43.0 as a primary or secondary [within four positions] diagnosis), and (3) the use of more than one of the following COPD medications at least twice per year (Figure 1). The mean age of COVID-19 patients was 47.9 years. Of them, 39.7% were males. Their mean mCCI was 0.9. COPD was present in 0.5% (n=35). The total medical cost was 4,736 USD during hospitalization. The mean hospital LOS were 23.0 days and the ICU admission rate was 3.2% for confirmed COVID-19. The overall mortality was 3.3% (Table 1).

2. COVID-19 patients in South Korea according to the underlying COPD

The mean age of the COPD group was significantly higher than that of the non-COPD group (71.3±11.6 years vs. 47.7±19.1 years, p<0.001). Of patients in the COPD group, 54.3% were males. The mCCI was higher in the COPD group than in the non-COPD group (2.6±1.9 vs. 0.8±1.3, p<0.001). Of COPD patients, 14.3% belonged to the medical aids group. For the COPD group, the total medical cost was 5,124 USD during hospitalization and the mean hospital LOS was 23.5 days. The ICU admission rate was 2.9% in COPD patients with confirmed COVID-19. There was no significant difference in hospital LOS or ICU admission rate between the two groups. However, mortality was higher in the COPD group than in the non-COPD group (22.9% vs. 3.2%, p<0.001) (Table 2).

3. Association between clinical outcomes and underlying COPD in COVID-19 patients

Univariable and multiple logistic regression analyses were used to examine effects of age, sex, mCCI, socioeconomic status, and previous COPD on the mortality and hospital LOS of COVID-19. Simple and multiple linear regression analyses were conducted to evaluate contributing factors to hospital LOS in COVID-19.

In univariable analyses, all variables (age, male sex, mCCI score, medical aids, and COPD) were associated with mortality. In multiple analyses, older age (odds ratio [OR], 1.12; 95% confidence interval [CI], 1.11–1.14), male sex (OR, 2.29; 95% CI, 1.67–3.12), higher mCCI scores (OR, 1.30; 95% CI, 1.20–1.41), and poor socioeconomic status (OR, 1.55; 95% CI, 1.03–2.32) remained significant associations with mortality. However, underlying COPD was not significantly associated with mortality of patients with COVID-19 in adjusted analysis (OR, 1.73; 95% CI, 0.67–4.47; p=0.259).

Underlying COPD was not a contributing factor of longer hospital LOS in univariable or multiple linear regression analysis. Age (standardized coefficient [β]=0.178), mCCI score

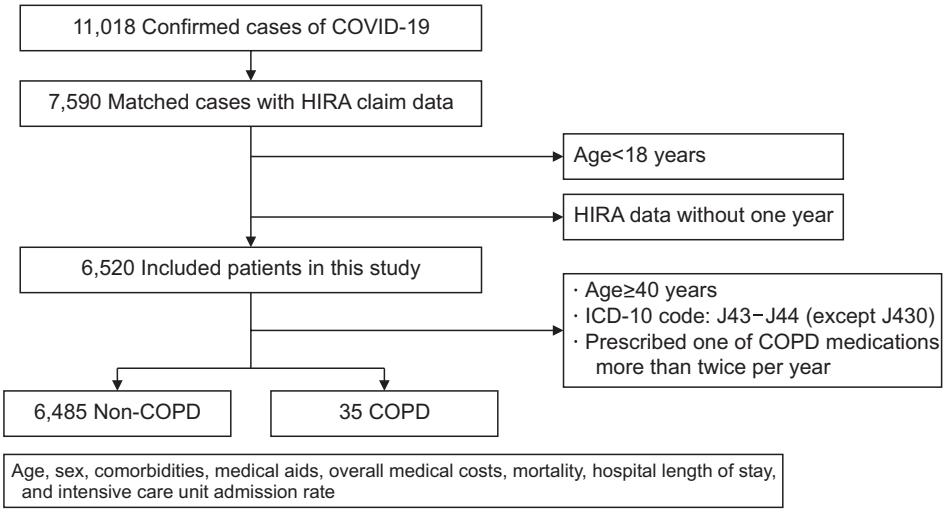

Figure 1. Flow chart showing the selection of subjects for this study. Confirmed cases of coronavirus disease 2019 (COVID-19) were linked to medical claims data of the Health Insurance Review and Assessment Service (HIRA) (n=7,590). Subjects younger than 18 years and those without HIRA data within 1 year were excluded. Ultimately, 6,520 patients with COVID-19 were included in this study. Groups were divided by the operational definition of chronic obstructive pulmonary disease (COPD). Thirty-five patients with underlying COPD were included. ICD-10: International Classification of Disease, 10th revision.

Table 1. Demographics of COVID-19 patients in South Korea

Characteristic	Total (n=6,520)
Age, yr	47.9±19.1
Male sex	2,587 (39.7)
Comorbidities	
Diabetes	1,043 (16.0)
Myocardial infarction	85 (1.3)
Congestive heart failure	179 (2.8)
Peripheral vascular disease	448 (6.9)
Cerebrovascular disease	392 (6.0)
Dementia	96 (1.5)
Rheumatic or connective tissue	134 (2.1)
Gastric or peptic ulcer	613 (9.4)
Hemiplegia or paraplegia	98 (1.5)
Chronic kidney disease	75 (1.5)
Any malignancy	212 (3.3)
Metastatic solid tumor	26 (0.4)
Immunodeficiency	3 (0.1)
mCCI score, points	0.9±1.3
Percentage of COPD	35 (0.5)
Percentage of inhaler use	
LAMA	11 (0.2)
LABA	-
LABA+LAMA	15 (0.2)
ICS (±LABA)	185 (2.8)
Medical aid insurance	583 (8.9)
Overall medical costs/patient, USD	4,736±5,902
Hospital length of stay, day	23.0±14.2
ICU admission rate	207 (3.2)
Mortality	216 (3.3)

Values are presented as mean±SD or number (%).
COVID-19: coronavirus disease 2019; mCCI: modified Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; LAMA: long-acting muscarinic antagonists; LABA: long-acting β-agonists; ICS: inhaled corticosteroid; ICU: intensive care unit; SD: standard deviation.

(β=0.079), and the status of medical aids (β=−0.048) were associated with hospital LOS. No multi-collinearity between variables was observed in the analyses.

COPD group was also not associated with ICU admission rate in univariate or multiple analysis. Older age (OR, 1.05; 95% CI, 1.04–1.06), male sex (OR, 1.98; 95% CI, 1.48–2.63), higher mCCI score (OR, 1.21; 95% CI, 1.11–1.31), and poor socioeconomic status (OR, 0.59; 95% CI, 0.36–0.98) were contributing factors of ICU admission rate of COPD patients with COVID-19 infection (Table 3).

Table 2. Differences of COVID-19 patients according to underlying COPD

	Non-COPD (n=6,485)	COPD (n=35)	p-value
Age, yr	47.7±19.1	71.3±11.6	<0.001
Male sex	2,568 (39.6)	19 (54.3)	0.077
mCCI score, points	0.8±1.3	2.6±1.9	<0.001
Medical aid insurance	578 (8.9)	5 (14.3)	0.264
Overall medical cost/patient, USD	4,726±5,898	5,124±4,802	0.691
Hospital length of stay, day	23.0±4.2	23.5±18.2	0.883
ICU admission rate	206 (3.2)	1 (2.9)	0.914
Mortality	208 (3.2)	8 (22.9)	<0.001

Values are presented as mean±SD or number (%).
COVID-19: coronavirus disease 2019; COPD: chronic obstructive pulmonary disease; mCCI: modified Charlson Comorbidity Index; ICU: intensive care unit; SD: standard deviation.

Discussion

We examined the association between underlying COPD and prognosis of COVID-19 infection in this nationwide retrospective population study and found that underlying COPD did not affect the prognosis of COVID-19 infection. Of 6,520 confirmed COVID-19 patients, 35 patients were diagnosed as COPD by well-defined operational definition[6-11]. Although the mortality of the COPD group was higher than that of the non-COPD group (22.9% vs. 3.2%, p<0.001) in the chi-square test, the association of COPD with COVID-19 mortality disappeared in adjusted analyses, suggesting that underlying COPD was not an independent factor of the mortality. On the other hand, accompanying situation of COPD patients such as older age and more comorbidities affected the mortality, not COPD itself.

Another interesting finding was the low prevalence but high mortality of COPD patients with confirmed COVID-19. Only 35 patients (0.5% of all COVID-19 patients) had COPD in this study. Their mortality exceeded 20%. This result is in line with a previous meta-analysis[13]. The potential reason for the low prevalence of COPD in COVID-19 patients might be because patients are so afraid of COVID-19 infection that they might reduce social activity and wear masks. As mentioned early in the discussion, higher mortality of COPD was associated with old age, male sex, the number of underlying comorbidities, and poor socioeconomic status, rather than COPD itself.

Previous studies had several limitations in that those studies

Table 3. Factors associated with clinical outcomes of COVID-19 according to underlying COPD

	Mortality				Hospital length of stay				ICU admission			
	Univariable		Multiple		Univariable		Multiple		Univariable		Multiple	
	OR (95% CI)	p-value	OR (95% CI)	p-value	B	p-value	β	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.13 (1.11–1.14)	<0.001	1.12 (1.11–1.14)	<0.001	0.207	<0.001	0.178	<0.001	1.06 (1.05–1.06)	<0.001	1.05 (1.04–1.06)	<0.001
Male sex	1.80 (1.37–2.36)	<0.001	2.29 (1.67–3.12)	<0.001	−0.018	0.149	−0.011	0.366	1.87 (1.41–2.46)	<0.001	1.98 (1.48–2.63)	<0.001
mCCI score	1.69 (1.58–1.81)	<0.001	1.30 (1.20–1.41)	<0.001	0.153	<0.001	0.079	<0.001	1.44 (1.34–1.54)	<0.001	1.21 (1.11–1.31)	<0.001
Medical aids	2.33 (1.63–3.34)	<0.001	1.55 (1.03–2.32)	0.035	−0.012	0.341	−0.048	<0.001	0.97 (0.59–1.58)	0.901	0.59 (0.36–0.98)	0.043
COPD	8.94 (4.01–19.92)	<0.001	1.73 (0.67–4.47)	0.259	0.002	0.850	−0.021	0.091	0.90 (0.12–6.58)	0.915	0.22 (0.03–1.67)	0.142

COVID-19: coronavirus disease 2019; COPD: chronic obstructive pulmonary disease; OR: odds ratio; CI: confidence interval; mCCI: modified Charlson Comorbidity Index.

did not have accurate information on pre-morbid comorbidities or medication[14]. Unlike that study, ours was a nationwide population study that included detailed comorbidity and medication information without bias or missing data. Consequently, we were able to precisely determine the underlying COPD and other confounding demographic factors.

This study has several limitations. First, data of this study did not include lung function or COPD symptom scores because of the nature of medical claims data. We could not analyze effects of the severity of COPD on COVID-19 in this study. Second, this was a retrospective study. However, a retrospective study using medical claims data was appropriate for this study because we had all information on medical utilization before the diagnosis of COVID-19. Third, we did not have data about mortality date of COVID-19 in the HIRA medical claim data. Therefore, the survival method which might increase the statistical power of this study could not be performed in the analysis.

In summary, this retrospective nationwide study showed that underlying COPD was not associated with a poor prognosis of COVID-19. Older age, male sex, higher mCCI scores, and poor socioeconomic status were significantly associated with mortality. Our results suggest that COPD patients do not have to worry about COVID-19 exaggeratedly.

Authors' Contributions

Conceptualization: Rhee CK, You KH, An TJ, Kim Y, Park YB. Methodology: Rhee CK, You KH. Formal analysis: Kim K, Cho DY. Data curation: Kim K, Cho DY. Software: Kim K, Cho DY. Validation: Rhee CK, You KH, Park YB. Investigation: Rhee CK, An TJ. Resources: Rhee CK, Kim K. Writing - original draft preparation: An TJ, Kim Y. Writing - review and editing: An TJ, Kim Y. Visualization: An TJ. Supervision: Rhee CK, You KH, Park YB. Project administration: Rhee CK. Funding acquisition: Rhee CK, You KH. Approval of final manuscript: all authors.

Conflicts of Interest

CK Rhee has received consulting/lecture fees from MSD, AstraZeneca, GSK, Novartis, Takeda, Mundipharma, Boehringer-Ingelheim, Teva, Sanofi, and Bayer. Other authors do not have any conflict of interests.

Funding

This research was supported by a grant (HI18C0522) from the Korea Health Technology R&D Project through the Korean Health Industry Development Institute (KHIDI) funded

by the Ministry of Health & Welfare, Republic of Korea.

Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

Supplementary Table S1. Modified Charlson's weighted index of comorbidities.

References

1. Leung JM, Niikura M, Yang CW, Sin DD. COVID-19 and COPD. Eur Respir J 2020;56:2002108.
2. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, et al. COVID-19 with different severities: a multicenter study of clinical features. Am J Respir Crit Care Med 2020;201:1380-8.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
4. Sin DD. COVID-19 in COPD: a growing concern. EClinicalMedicine 2020;26:100546.
5. Kim L, Kim JA, Kim S. A guide for the utilization of Health Insurance Review and Assessment Service National Patient Samples. Epidemiol Health 2014;36:e2014008.
6. Rhee CK, Kim K, Yoon HK, Kim JA, Kim SH, Lee SH, et al. Natural course of early COPD. Int J Chron Obstruct Pulmon Dis 2017;12:663-8.
7. Park SC, Kim YS, Kang YA, Park EC, Shin CS, Kim DW, et al. Hemoglobin and mortality in patients with COPD: a nationwide population-based cohort study. Int J Chron Obstruct Pulmon Dis 2018;13:1599-605.
8. Lim JU, Kim K, Kim SH, Lee MG, Lee SY, Yoo KH, et al. Comparative study on medical utilization and costs of chronic obstructive pulmonary disease with good lung function. Int J Chron Obstruct Pulmon Dis 2017;12:2711-21.
9. Lee J, Lee JH, Kim JA, Rhee CK. Trend of cost and utilization of COPD medication in Korea. Int J Chron Obstruct Pulmon Dis 2017;12:27-33.
10. Kim JA, Lim MK, Kim K, Park J, Rhee CK. Adherence to inhaled medications and its effect on healthcare utilization and costs among high-grade chronic obstructive pulmonary disease patients. Clin Drug Investig 2018;38:333-40.
11. Jo YS, Kim YH, Lee JY, Kim K, Jung KS, Yoo KH, et al. Impact of BMI on exacerbation and medical care expenses in subjects with mild to moderate airflow obstruction. Int J Chron Obstruct Pulmon Dis 2018;13:2261-9.
12. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57:1288-94.
13. Alqahtani JS, Oyelade T, Aldhahir AM, Alghamdi SM, Almehmadi M, Alqahtani AS, et al. Prevalence, severity and mortality associated with COPD and Smoking in patients with COVID-19: a rapid systematic review and meta-analysis. PLoS One 2020;15:e0233147.
14. Halpin DM, Singh D, Hadfield RM. Inhaled corticosteroids and COVID-19: a systematic review and clinical perspective. Eur Respir J 2020;55:2001009.