# COPD is a Risk Factor for COVID-19, But Does Not Confer Increased Severity of the Disease

**Jae Seok Jeong**
Jeonbuk National University Medical School
**Jong Seung Kim**
Jeonbuk National University Medical School
**Yeon Seok You**
Jeonbuk National University Medical School
**Sang Woo Yeom**
Jeonbuk National University
**Yong Chul Lee** ( leeyc@jbnu.ac.kr )
Jeonbuk National University Medical School

**Research Article**

**Keywords:** COPD, COVID-19, disease, risk

**Posted Date:** May 13th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-497997/v1



**Version of Record:** A version of this preprint was published at Respiratory Medicine on November 1st, 2021. See the published version at https://doi.org/10.1016/j.rmed.2021.106640.

# Abstract

Epidemiologic studies suggest that COPD is associated with an increased risk of poor outcome in patients with COVID-19, although they failed to demonstrate COPD as a risk factor for acquiring COVID-19. However, most data have come from a limited global population. In this nationwide cohort study based on the Korean national health insurance claims-based database, COPD is associated with increased risk for COVID-19 and having COPD does not seem to confer substantial risk for severe COVID-19 and mortality. These findings indicate that heterogeneity in the populations across many countries may complicate the net effects of COPD on the COVID-19-related outcomes.


# Introduction

In the period up to April 2021, the coronavirus disease (COVID-19) pandemic associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected approximately 143,000,000 people globally with over 3,000,000 deaths, and poses a great threat to patients with chronic lung diseases (1). However, evaluating the excess risk of chronic obstructive pulmonary disease (COPD) for COVID-19 and, in particular, for more severe disease, is challenging (2). Initially, the prevalence of COPD among hospitalized patients with COVID-19 has been reported to be lower than in the general population and in those reported with other comorbidities (3), a finding contrary to the common speculation that COPD may be more susceptible to contracting respiratory viruses. Paradoxically, COVID-19 in COPD is increasingly associated with critical illness of COVID-19 (2, 4). A nationwide analysis on the comorbidity of 1590 COVID-19 patients in China showed that COPD was a risk factor for reaching the composite end points related to poorer clinical outcomes (5). These findings indicate the heterogeneity of clinical COVID-19 cohorts across different nations and the clinical severity with diverse comorbidities (2).

The aim of this study is to determine whether COPD influences the occurrence and clinical severity of COVID-19.

# Methods

This large-scale cohort covers individuals who underwent SARS-CoV-2 testing in South Korea from January 1, 2020 to May 1, 2020 supported by the Korean Centers for Disease Control and the National health insurance service (NHIS). For each patient who underwent SARS-CoV-2 testing, we combined medical data on COVID-19-related outcomes during the hospitalization with claim-based data from January 1, 2015 to May 1, 2020, including personal data (age, sex, region of residence, and socioeconomic status) and health care records of inpatients and outpatients throughout the past 5 years (including health care visits, prescriptions, diagnoses, and procedures), retrospectively. SARS-CoV-2 infection was defined by a positivity on a real-time RT–PCR assay of nasal or pharyngeal swabs (6). A history of COPD (J43-J44, apart from J430), diabetes mellitus (E10-14), ischemic heart disease (I20-25), cerebrovascular disease (I60-64, I69, and G45), hypertension (I10-13 and I15), or chronic kidney disease (N18-19) was defined by the physician diagnosis reporting of at least two claims within 1 year during this

5-year study period according to the appropriate International Classification of Disease, Tenth Revision (ICD-10) code (7). In this study, “exposure” comprised the development of COPD; the “primary outcome” was test positivity for SARS-CoV-2 among all patients who underwent SARS-CoV-2 testing, and the “secondary outcome” was severe disease or mortality of patients who tested positive for SARS-CoV-2. The definition of severe disease included: 1) requirement for oxygen supplementation, 2) intensive care units (ICU) admission, 3) intubation with mechanical ventilation, or 4) application of extracorporeal membrane oxygenation (ECMO).

We performed two rounds of propensity score matching to balance the baseline characteristics and to reduce potential confounders. We evaluated each propensity score matching in a 1:1 ratio using the ‘greedy nearest-neighbor’ algorithm and calculated the predicted probability of (a) individuals with a history of COPD versus individuals without a history of COPD among all patients who underwent SARS-CoV-2 testing (n = 129,120); (b) individuals with a history of COPD versus individuals without a history of COPD among patients with confirmed COVID-19 (n = 8,070). The adequacy of matching was evaluated by comparing the distributions of propensity score and standardized mean differences (SMDs). After utilizing a multivariate logistic regression model adjusted for history of angina, any type of cancer, hypertension (HTN), congestive heart failure (CHF), chronic kidney disease (CKD), cerebrovascular disease (CVD), diabetes mellitus (DM), hepatitis, and myocardial infarction (MI), estimation of the adjusted odds ratios (aORs) with 95% CIs was performed. Patient-related data were anonymized and the protocol was approved by the Institutional Review Board of Jeonbuk National University Hospital (2020-04-067).

# Results

Among 129,120 patients who underwent SARS-CoV-2 testing (mean age ± SD, 41.7 ± 19.6 years), we identified 8,070 (6.25%) patients who tested positive (all SMDs < 0.1). There were 4,800 patients with a history of COPD in the entire cohort (n = 129,120). Then, we performed 1:1 propensity score matching in the full-unmatched cohort and identified 4,800 patients without a history of COPD (**Table 1**, all SMDs < 0.05). Among all patients tested, the positivity rate of SARS-CoV-2 testing in patients with COPD was 7.3% (350/4800), compared with 4.8% (230/4800) in those without COPD (aOR, 1.54; 95% CI, 1.3–1.83) (**Table 1 and Fig. 1**). Furthermore, we identified 350 patients with COPD among the patients who tested positive for SARS-CoV-2 (n = 8,070). We also performed 1:1 propensity score matching in the full-unmatched cohort and identified 350 patients with no history of COPD (Table 2, all SMDs < 0.1). The rate of severe disease in patients with COPD was 28.9% (101/350) among patients who tested positive for SARS-CoV-2, compared with 25.1% (88/350) in those without COPD (aOR, 1.23; 95% CI, 0.85–1.76). In particular, among patients confirmed to have COVID-19, the rate of mortality in patients with COPD was 17.7% (62/350), compared with 13.7% (48/350) in those without COPD (aOR, 1.39; 95% CI, 0.87–2.23) (Table 2 **and Fig. 1**).

# Discussion

Herein, we have identified that COPD is associated with an increased risk for COVID-19. Moreover, having COPD does not seem to confer a substantial risk for severe disease and mortality. These are interesting in that the results from numerous epidemiologic studies have suggested that COPD is associated with an increased risk of poor outcome in patients with COVID-19, although they failed to clearly demonstrate COPD as a risk factor for acquiring COVID-19 (2, 4). Since most data so far that can potentially explain the relationship between COPD and SARS-CoV-2 in the emergence of COVID-19 has come from a limited global population, the data will inevitably involve heterogeneous patients having different proportions of medical comorbidities under the variability in testing and admission strategies (2), and this may obscure the effect of COPD on contracting COVID-19. Indeed, increased angiotensin-converting enzyme-2, an entry protein for SARS-CoV-2, was observed in the airways of COPD patients who smoke, a similar finding that favors the potential implication of COPD as a risk factor for COVID-19 (8).

Furthermore, once a host has become infected with SARS-CoV-2 in the airways, a unique phenotype of systemic immune/inflammatory responses has been reported to be associated with COVID-19 acute respiratory distress syndrome (ARDS) compared to their non-COVID-19 counterparts, although patients with COVID-19 had less severe ARDS initially (9). In the same context, excluding respiratory diseases, most comorbidities were associated with an increased risk of COVID-19-related death (10). These findings suggest that systemic general medical conditions shaping overall immune/inflammatory responses are critically implicated in the regulation of the clinical course of COVID-19, even to a greater extent than the medical conditions involving the respiratory tract itself.

Although we could not define the various phenotypes of COPD (2) and obtain information on smoking status and treatment modalities for COPD (11, 12, 13) because data were claim-based, our findings suggest that COPD may be associated with an increased risk for COVID-19 and having COPD does not seem to confer a substantial risk for severe COVID-19 and mortality.

# Declarations

### Author Contributions:

J.S.J. conceived and designed the research, interpreted the data, and wrote the manuscript. J.S.K. conceived and designed the research, collected the data and performed the analysis. Y.C.L. conceived and designed the research, interpreted the data, and edited the manuscript Y.S.Y. and S.W.Y. data curation, formal analysis.

### Declaration of All Sources of Funding:

This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (NRF-2020R1A2C2101942; Y.C.L.), and by the fund of Biomedical Research Institute, Jeonbuk National University Hospital. No competing financial interests exist.

# References


1. Coronavirus Worldometer. https://www.worldometers.info/coronavirus/ Date last accessed: 15 March 2021.
2. Leung JM, Niikura M, Yang CWT, Sin DD. COVID-19 and COPD. Eur Respir J. 2020;56:2002108.
3. Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A. Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? Lancet Respir Med. 2020;8:436–438.
4. Simons SO, Hurst JR, Miravitlles M, Franssen FME, Janssen DJA, Papi A, Duiverman ML, Kerstjens HAM. Caring for patients with COPD and COVID-19: a viewpoint to spark discussion. Thorax. 2020;75:1035–1039.
5. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, Liu XQ, Chen RC, Tang CL, Wang T, Ou CQ, Li L, Chen PY, Sang L, Wang W, Li JF, Li CC, Ou LM, Cheng B, Xiong S, Ni ZY, Xiang J, Hu Y, Liu L, Shan H, Lei CL, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Cheng LL, Ye F, Li SY, Zheng JP, Zhang NF, Zhong NS, He JX; China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55:2000547.
6. World Health Organization. Diagnostic testing for SARS-CoV-2: Interim guidance. September 11, 2020. Assessed January 4, 2021. https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2.
7. Yang JM, Koh HY, Moon SY, Yoo IK, Ha EK, You S, Kim SY, Yon DK, Lee SW. Allergic disorders and susceptibility to and severity of COVID-19: A nationwide cohort study. J Allergy Clin Immunol. 2020;146:790–798.
8. Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, Dorscheid DR, Sin DD. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. Eur Respir J. 2020;55:2000688.
9. Hue S, Beldi-Ferchiou A, Bendib I, Surenaud M, Fourati S, Frapard T, Rivoal S, Razazi K, Carteaux G, Delfau-Larue MH, Mekontso-Dessap A, Audureau E, de Prost N. Uncontrolled innate and impaired adaptive immune responses in patients with COVID-19 Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2020;202:1509–1519.
10. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584:430–436.
11. Polverino F. Cigarette smoking and COVID-19: A complex interaction. Am J Respir Crit Care Med. 2020;202:471–472.
12. Schultze A, Walker AJ, MacKenna B, Morton CE, Bhaskaran K, Brown JP, Rentsch CT, Williamson E, Drysdale H, Croker R, Bacon S, Hulme W, Bates C, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn

J, McDonald HI, Tomlinson L, Mathur R, Wing K, Wong AYS, Forbes H, Parry J, Hester F, Harper S, Evans SJW, Quint J, Smeeth L, Douglas IJ, Goldacre B; OpenSAFELY Collaborative. Risk of COVID-19-related death among patients with chronic obstructive pulmonary disease or asthma prescribed inhaled corticosteroids: an observational cohort study using the OpenSAFELY platform. Lancet Respir Med. 2020;8:1106–1120.

13. Finney LJ, Glanville N, Farne H, Aniscenko J, Fenwick P, Kemp SV, Trujillo-Torralbo MB, Loo SL, Calderazzo MA, Wedzicha JA, Mallia P, Bartlett NW, Johnston SL, Singanayagam A. Inhaled corticosteroids downregulate the SARS-CoV-2 receptor ACE2 in COPD through suppression of type I interferon. J Allergy Clin Immunol. 2020 Oct 15:S0091-6749(20)31407-X.

# Tables

**Table 1. Baseline demographics for all severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) tested patients in South Korea (N=129,120).**

| | Patient who underwent SARS-CoV-2 test (total n = 129120) | | | | |
|---|---|---|---|---|---|
| | COPD | | | | |
| characteristic | No | | Yes | | SMD |
| Total, n (%) | 4800 | | 4800 | | |
| Age, mean  SD | 62.7 | 15.6 | 62.4 | 15.6 | 0.018 |
| Sex, n (%) | | | | | 0.024 |
| Male | 2427 | (50.6) | 2484 | (51.7) | |
| Female | 2373 | (49.4) | 2316 | (48.3) | |
| Social economic status, n (%) | | | | | 0.006 |
| Low | 3048 | (63.5) | 3061 | (63.8) | |
| High | 1752 | (36.5) | 1739 | (36.2) | |
| History of Angina, n (%) | 1307 | (27.2) | 1290 | (26.9) | 0.008 |
| History of Cancer, n (%) | 1145 | (23.9) | 1188 | (24.8) | 0.021 |
| History of HTN, n (%) | 1065 | (22.2) | 1064 | (22.2) | 0.001 |
| History of CHF, n (%) | 482 | (10.0) | 518 | (10.8) | 0.001 |
| History of CKD, n (%) | 993 | (20.7) | 999 | (20.8) | 0.025 |
| History of CVD, n (%) | 1010 | (21.0) | 994 | (20.7) | 0.003 |
| History of diabetes mellitus, n (%) | 652 | (13.6) | 674 | (14.0) | 0.008 |
| History of hepatitis, n (%) | 1402 | (29.2) | 1401 | (29.2) | 0.013 |
| History of MI, n (%) | 371 | (7.7) | 406 | (8.5) | 0.001 |
| COVID-19, n (%) | 230 | (4.79) | 350 | (7.29) | |
| Minimally adjusted OR (95% CI) | Reference | | 1.55 | (1.3-1.83)*** | |
| Fully adjusted OR (95% CI) | Reference | | 1.54 | (1.3-1.83)*** | |

*Abbreviations:* CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; SMD, standardized mean difference.
***: Statistically significant

**Table 2. Baseline characteristics of propensity score-matching group (no previous COPD versus COPD groups) with laboratory confirmed COVID-19 in a Korean nationwide cohort.**

| | Patient who tested positive for SARS-CoV-2 test (total n = 8070) | | | | |
|---|---|---|---|---|---|
| | Influenza | | | | |
| characteristic | No | | Yes | | SMD |
| Total, n (%) | 350 | | 350 | | |
| Age, mean  SD | 62.5 | 15.5 | 62.3 | 15.9 | 0.011 |
| Sex, n (%) | | | | | 0.040 |
| Male | 166 | (47.4) | 173 | (49.4) | |
| Female | 184 | (52.6) | 177 | (50.6) | |
| Social economic status, n (%) | | | | | 0.050 |
| Low | 252 | (72.0) | 244 | (69.7) | |
| High | 98 | (28.0) | 106 | (30.3) | |
| History of Angina, n (%) | 98 | (28.0) | 104 | (29.7) | 0.038 |
| History of Cancer, n (%) | 86 | (24.6) | 81 | (23.1) | 0.034 |
| History of HTN, n (%) | 92 | (26.3) | 95 | (27.1) | 0.019 |
| History of CHF, n (%) | 39 | (11.1) | 43 | (12.3) | 0.036 |
| History of CKD, n (%) | 79 | (22.6) | 84 | (24.0) | 0.034 |
| History of CVD, n (%) | 79 | (22.6) | 82 | (23.4) | 0.020 |
| History of diabetes mellitus, n (%) | 46 | (13.1) | 46 | (13.1) | 0.001 |
| History of hepatitis, n (%) | 82 | (23.4) | 93 | (26.6) | 0.073 |
| History of MI, n (%) | 36 | (10.3) | 44 | (12.6) | 0.072 |
| Severe clinical outcomes of COVID-19 | 88 | (25.1) | 101 | (28.9) | |
| Minimally adjusted OR (95% CI) | Reference | | 1.22 (0.85-1.74) | | |
| Fully adjusted OR (95% CI) | Reference | | 1.23 (0.85-1.76) | | |
| Death | 48 | (13.7) | 62 | (17.7) | |
| Minimally adjusted OR (95% CI) | Reference | | 1.35 (0.87-2.11) | | |
| Fully adjusted OR (95% CI) | Reference | | 1.39 (0.87-2.23) | | |

*Abbreviations:* CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; SMD, standardized mean difference. ***: statistically significant

# Figures

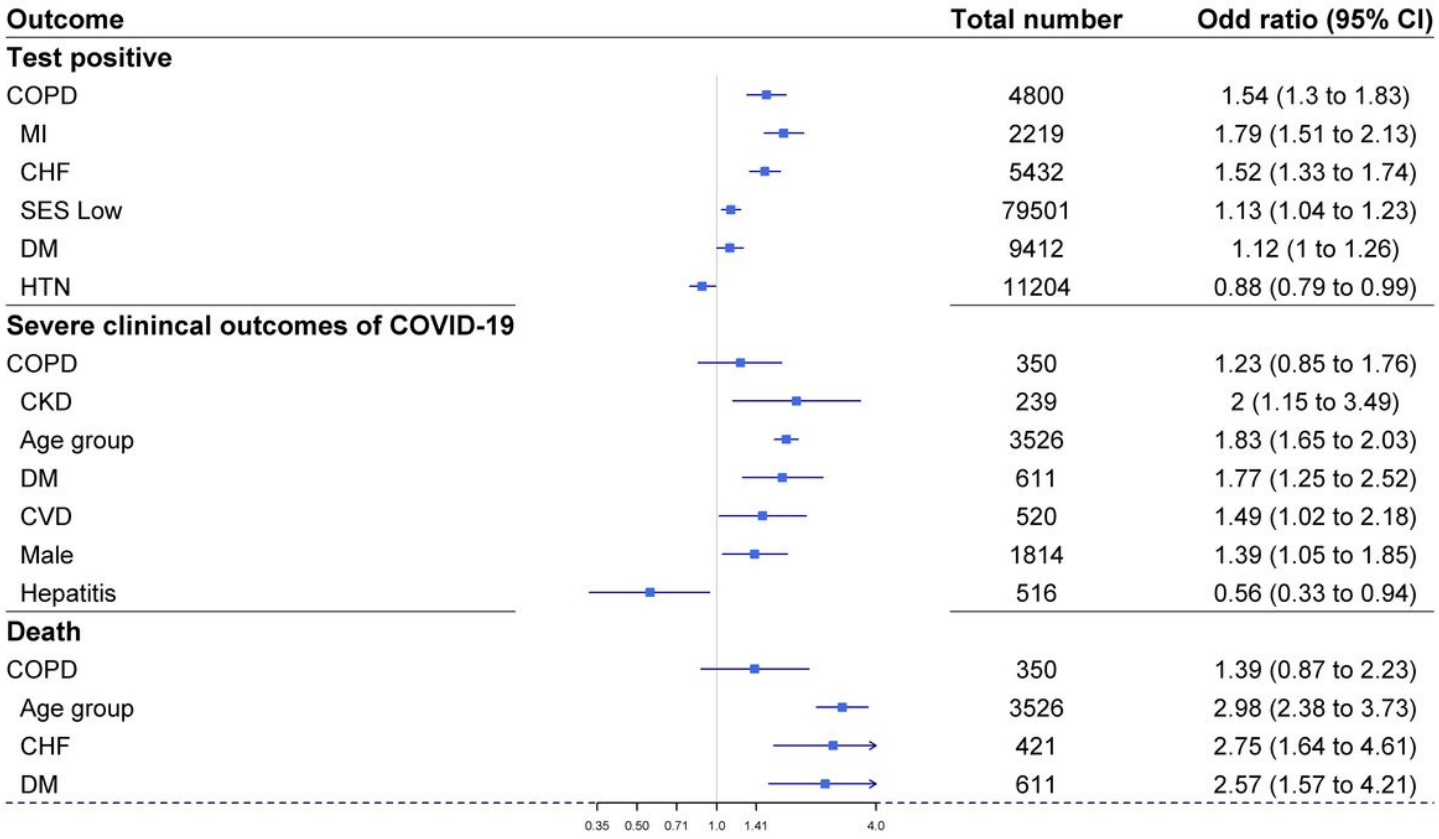


**Figure 1**

Propensity score-matched association of chronic obstructive pulmonary disease (COPD) with test positivity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (primary outcome) among all patients who underwent SARS-CoV-2 testing (n = 129,120) and the association of COPD with severe disease and mortality (secondary outcome) among patients with confirmed coronavirus disease (COVID-19) (n = 8,070). CHF, congestive heart failure; CKD, chronic kidney disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction ; SES, socioeconomic status.