


# Clinical course and outcomes of COVID-19 patients with chronic obstructive pulmonary disease

## A retrospective observational study in Wuhan, China

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### Abstract

Information about coronavirus disease 2019 (COVID-19) patients with pre-existing chronic obstructive pulmonary disease (COPD) is still lacking. The aim of this study is to describe the clinical course and the outcome of COVID-19 patients with comorbid COPD.

This retrospective study was performed at Wuhan Huoshenshan Hospital in China. Patients with a clear diagnosis of COVID-19 who had comorbid COPD (N = 78) were identified. COVID-19 patients without COPD were randomly selected and matched by age and sex to those with COPD. Clinical data were analyzed and compared between the two groups. The composite outcome was the onset of intensive care unit admission, use of mechanical ventilation, or death during hospitalization. Multivariable Cox regression analyses controlling for comorbidities were performed to explore the relationship between comorbid COPD and clinical outcome of COVID-19.

Compared to age- and sex-matched COVID-19 patients without pre-existing COPD, patients with pre-existing COPD were more likely to present with dyspnea, necessitate expectorants, sedatives, and mechanical ventilation, suggesting the existence of acute exacerbations of COPD (AECOPD). Greater proportions of patients with COPD developed respiratory failure and yielded poor clinical outcomes. However, laboratory tests did not show severer infection, over-activated inflammatory responses, and multi-organ injury in patients with COPD. Kaplan–Meier analyses showed patients with COPD exhibited longer viral clearance time in the respiratory tract. Multifactor regression analysis showed COPD was independently correlated with poor clinical outcomes.

COVID-19 patients with pre-existing COPD are more vulnerable to AECOPD and subsequent respiratory failure, which is the main culprit for unfavorable clinical outcomes. However, COPD pathophysiology itself is not associated with over-activated inflammation status seen in severe COVID-19.

**Abbreviations:** ACE2 = angiotensin-converting enzyme 2, AECOPD = acute exacerbations of COPD, AKI = acute kidney injury, ALT = alanine transaminase, ARDS = acute respiratory distress syndrome, AST = aspartate aminotransferase, BNP = brain natriuretic peptide, CHD = coronary heart disease, COPD = chronic obstructive pulmonary disease, COVID-19 = Coronavirus disease 2019, CT = computerized tomography, cTnI = cardiac troponin I, DIC = disseminated intravascular coagulation, ICU = intensive care unit, MODS = multiple organ dysfunction syndrome, SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2, SIC = sepsis-induced coagulopathy; TBIL = total bilirubin, ULN = upper limit unit.

**Keywords:** clinical course, clinical outcome, COPD, COVID-19, SARS-CoV-2

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YB, LW, and YZ contribute equally to this work.

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The original data will be made available by corresponding authors under reasonable request, without undue reservation.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## 1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) still remains pandemic.<sup>[1]</sup> Up to August 2021, World Health Organization (WHO) reported over 4.2 million death cases.<sup>[2]</sup> Clinical outcomes including mortality, were worse in males, the elderly, and those with comorbidities including hypertension, diabetes, and cardiovascular disease.<sup>[3]</sup> As a common senile disease, chronic obstructive pulmonary disease (COPD) is another comorbidity among patients hospitalized with COVID-19.<sup>[4]</sup> A series of meta-analyses<sup>[5–7]</sup> and retrospective studies<sup>[4,8–13]</sup> have shown that comorbid COPD was correlated with the severity and mortality of COVID-19. Nevertheless, the clinical characteristics of COVID-19 patients with COPD and the impact of COPD on the clinical course and outcomes of the disease have not yet been well delineated.

Prior reports have indicated that COVID-19 patients with comorbid COPD were more likely to be male, with older age and more comorbidities, than those without COPD.<sup>[8,9,11,12]</sup> Nevertheless, the influence of differences in these demographical features between COVID-19 patients with and without COPD has not been considered yet. To examine the impact of the pathophysiology of COPD on the clinical course of COVID-19, clinical data of COVID-19 patients with pre-existing COPD hospitalized at Wuhan Huoshenshan Hospital and age- and sex-matched COVID-19 patients without COPD randomly selected from the same cohort were compared. The association of comorbid COPD with clinical outcomes of COVID-19 was also explored *via* multivariable stepwise Cox regression.

## 2. Methods

### 2.1. Study participants

In this single-center retrospective observational study, a total of 2994 consecutive patients hospitalized in Wuhan Huoshenshan Hospital from February 5 to March 15, 2020 were screened and assessed. The inclusion criteria were:

1. patients with confirmed diagnosis of COVID-19 by detection of SARS-CoV-2 via real-time PCR according to World Health Organization interim guidelines<sup>[14]</sup>; and
2. patients with intact clinical data.

This tertiary hospital, located in the province of Hubei, was assigned to treat COVID-19 patients by the Chinese government during the outbreak of this pandemic. To avoid the influence of pathophysiology of other respiratory diseases, patients with pre-existing bronchiectasis, bronchial asthma, pulmonary tuberculosis, interstitial lung disease, and pulmonary bulla were excluded from this analysis (Fig. 1).

A total of 78 COVID-19 patients were diagnosed with COPD (ICD code: J44) by a physician based on prior electronic medical records or the report of the patients themselves and their family members. Compared with the overall population in the cohort, those with COPD had a significant older age (median [IQR], 70.5 [65.3–79.8] vs 60.0 [49.0–68.0];  $P < .001$ ) and had a significant higher proportion of male sex (71.8% vs 51.1%;  $P < .001$ ). Prior studies has shown that both male sex and older age are independently correlated with in-hospital death in COVID-19 patients.<sup>[15]</sup> Considering this, an age- ( $\pm 2$  years) and sex-matched patient without COPD was randomly selected for each patient in the COPD group in order to adjust for age and sex

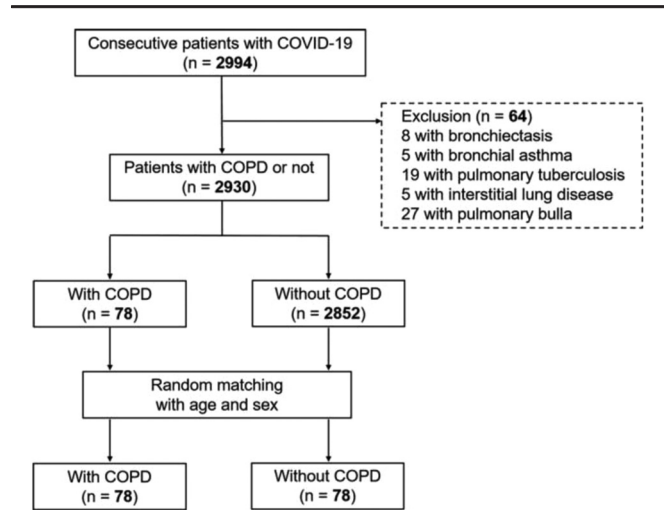


Figure 1. Flowchart of patient recruitment.

according to the method described before.<sup>[16]</sup> If there were several non-COPD patients available for one patient with COPD, a match was randomly made from these available candidate patients. In total, we enrolled 156 COVID-19 patients into this study and collected their data retrospectively (Fig. 1). The present study approved by the Ethics Committee of Wuhan Huoshenshan hospital (K202101-02).

### 2.2. Data collection

All clinical data were collected from the electronic medical records by two physicians (Y Bai and L Wen), and independently checked by another two researchers (Y Zhao and J Li). Clinical data acquired herein included demographics (i.e., age, sex, and pre-existing diseases), initial symptoms (e.g., fever, myalgia, fatigue, and cough), vital signs (i.e., heart rate, blood pressure, body temperature, and respiratory rate), initial computerized tomography (CT) scan data, laboratory parameters (i.e., infection-related indices, blood routine test, coagulation function markers, myocardial impairment markers, liver function indices, kidney function indices, electrolytes, and glucose), and complications (e.g., cardiac insufficiency and respiratory failure). For imaging data, infection volume was measured using a simple CT post-processing tool, and expressed in cubic centimeters.<sup>[17]</sup>

In addition, clinical data concerning therapeutics were also collected. In accordance with the WHO interim guidelines,<sup>[14]</sup> the patients were given individualized systematic treatments, including oxygen support, antivirals, secondary infection control, immune-modulators, and multi-organ support. Oxygen therapy was the key therapeutic approach among these treatments, which was administrated through nasal cannulas (normal or high-flow) and mechanical ventilation (non-invasive or invasive). For the treatment of COPD, anti-asthmatics included muscarinic antagonists (long-acting or short-acting), beta-2 agonists (long-acting or short-acting), inhaled corticosteroid, leukotriene receptor antagonist, phosphodiesterase-4 inhibitors, while expectorants included acetylcysteine, ambroxol, and eucalyptus enteric soft capsules.

A composite endpoint consisting of unfavorable clinical outcomes was adopted as the primary outcome, which included

the occurrence of admission to intensive care unit (ICU), use of mechanical ventilation, or death. Secondary outcomes included the occurrence of virus clearance, disease progression, disease deterioration, and death. The patients were followed-up until discharge from hospital after recovery or death. The duration from symptom onset to hospital admission, virus clearance, disease progression, disease deterioration, death, or the composite endpoint was also recorded.

### 2.3. Definitions

The diagnosis of COVID-19 was based on the WHO interim guidance.<sup>[14]</sup> Disease severity was determined according to the guideline for the diagnosis and management of COVID-19 (6th edition) published by the National Health Commission of China.<sup>[18]</sup> Disease progression and deterioration were defined as the exacerbation of disease from non-severe types (including both mild and moderate types) to severe type and critical type, respectively. Viral clearance was considered with three consecutive negative nucleic acid results from respiratory tract specimens produced with sampling intervals more than 24 hours.

The occurrence of complications was made according to the following standards. Anemia was diagnosed with haemoglobin  $\leq 110$  g/L. The diagnosis of myocardial injury was made with the serum levels of CKMB or cardiac troponin I (cTnI) exceeding the upper limit of normal (ULN).<sup>[19]</sup> Liver injury was diagnosed with the total bilirubin (TBIL) level more than twofold the ULN, or the serum levels of alanine transaminase (ALT) or aspartate aminotransferase (AST) more than threefold the ULN.<sup>[20]</sup> Hypoproteinemia was determined by the serum albumin level less than 25 g/L.<sup>[15]</sup> The occurrence of acute kidney injury (AKI) was confirmed by an increase in serum creatinine levels to more than 1.5 times the baseline.<sup>[21]</sup> Disseminated intravascular coagulation (DIC) and sepsis-induced coagulopathy (SIC) were determined by the International Society of Thrombosis and Haemostasis scoring systems.<sup>[22,23]</sup> Cardiac insufficiency was reported if the serum level of brain natriuretic peptide (BNP) exceeded the normal range, together with the presence of dyspnea, orthopnea, and edema of lower-extremity.<sup>[24]</sup> Hepatic failure was diagnosed in accordance with clinical practical guidelines on the management of acute liver failure released by European Association for the Study of the Liver.<sup>[25]</sup> Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition.<sup>[26]</sup> The diagnosis of respiratory failure was made by an arterial partial pressure of oxygen of  $<60$  mmHg. Multiple organ dysfunction syndrome (MODS) and shock were defined based on the multiple organ dysfunction score<sup>[27]</sup> and the 2016 Third International Consensus Definition for Sepsis and Septic Shock,<sup>[28]</sup> respectively.

### 2.4. Statistical analysis

For variables with missing data, no imputation was performed. Data is expressed as percentages (%) for enumeration data or medians (interquartile ranges [IQRs]) for quantitative data. Intergroup comparisons between COPD group and non-COPD group were performed using the  $\chi^2$  test (or Fisher's exact test) for enumeration data or the Mann-Whitney *U* non-parametric test for quantitative data. Cumulative survival curves were plotted using the Kaplan-Meier method together with the log-rank test.

Cox regression analyses were performed to determine if pre-existing COPD was an independent predictor for the primary

outcome. Since the aim of this study was to document the relationship between demographic variables and the clinical outcome of COVID-19, age, sex and pre-existing diseases were included in the univariable analysis. Then, three variables, that is, age, coronary heart disease (CHD), and COPD, were incorporated into the multivariable model based on the results of univariable analyses and their clinical merits mentioned in previous findings.<sup>[15,29-31]</sup> Atrial fibrillation and chronic kidney disease were excluded from the multifactor model owing to the small number of events. All statistical analyses were made using SPSS software (version 22.0, IBM Corp, NY).  $P < .05$  were considered statistically significant.

## 3. Results

### 3.1. Identification of COVID-19 patients with COPD

A total of 2994 consecutive hospitalized patients with a clear diagnosis of COVID-19 were screened from the medical record system. Among them, 8 patients with bronchiectasis, 5 patients with bronchial asthma, 19 patients with pulmonary tuberculosis, 5 patients with interstitial lung disease, and 27 patients with pulmonary bulla (diagnosed in previous health examinations or on admission) were excluded. Finally, 78 patients with pre-existing COPD were included (Fig. 1). Of these 78 patients, 6 cases were at acute attack phase and 2 cases had developed pulmonary heart disease. The median interval from the diagnosis of COPD to admission due to COVID-19 was 10.0 years (IQR, 7.3–20.0 years).

### 3.2. Demographic and clinical features

Demographic and clinical features of COVID-19 patients in the COPD group and the non-COPD group were indicated in Table 1. After matching, no difference could be seen in the prevalence of pre-existing diseases, such as hypertension and CHD ( $P > .05$ ) between the COPD group and the non-COPD group. Unexpectedly, no significant difference in disease severity was observed in the two groups (62.8% in COPD group vs 61.5% in non-COPD group;  $P = .868$ ). Concerning initial symptoms and signs, dyspnea occurred more frequently in those with than without COPD (59.0% vs 37.2%;  $P < .01$ ). For vital signs, there was a trend towards increased initial (87.0 [79.8–98.0] vs 82.5 [77.8–94.0] beats per min;  $P = .081$ ) and peak (107.5 [98.0–115.0] vs 102.0 [98.0–112.0] beats per min;  $P = .087$ ) HR during hospitalization in patients with COPD. Importantly, no significant difference in pulmonary infection volume and proportion (both  $P > .05$ ) was seen between these groups.

### 3.3. Laboratory findings

No significant difference in initial laboratory parameters (Table 2), including infection-related indicators, blood routine test, coagulation function biomarkers, myocardial damage markers, liver and kidney function indices, electrolytes, and glucose (all  $P > .05$ ), were observed between patients with COPD and without COPD. In addition to initial laboratory values, the maximum or minimum values of some indicators during hospitalization of utmost importance for the diagnosis of complications were also collected and analyzed. Those with COPD vs those without COPD only had a higher level of peak IL-6 (5.6 [2.6–29.9] vs 3.0 [1.5–7.7] pg/mL;  $P = .017$ ). No significant difference in peak or lowest value of other indicators

**Table 1**  
Demographic and clinical features of matched COVID-19 patients with and without COPD.

	Patients with COPD (n = 78)	Patients without COPD (n = 78)	P*
Age, y	70.5 (64.8–80.5)	70.5 (64.8–80.5)	.992
Male, No. (%)	55 (70.5)	55 (70.5)	1.000
Symptom onset to admission, d	29.0 (14.5–45.0)	22.0 (15.8–40.0)	.234
Comorbidity, No. (%)			
Hypertension	31 (39.7)	28 (35.9)	.620
Diabetes	6 (7.7)	14 (17.9)	.055
CHD	15 (19.2)	15 (19.2)	1.000
AF	5 (6.4)	1 (1.3)	.210*
CVD	5 (6.4)	5 (6.4)	1.000
CKD	2 (2.6)	1 (1.3)	1.000*
Malignancy	4 (5.1)	6 (7.7)	.513*
Disease classification, No. (%)			
Non-severe group	49 (62.8)	48 (61.5)	.868
Severe group	29 (37.2)	30 (38.5)	
Severe type	22 (28.2)	29 (37.2)	
Critical type	7 (9.0)	1 (1.3)	
Initial symptoms and signs, No. (%)			
Asymptomatic	4 (5.1)	6 (7.7)	.513
Fever	51 (65.4)	52 (66.7)	.866
Max. Temp, °C	38.3 (37.7–38.9)	38.5 (38–38.8)	.233
Chill	13 (16.7)	14 (17.9)	.832
Myalgia	28 (35.9)	18 (23.1)	.079
Fatigue	42 (53.8)	32 (41.0)	.109
Respiratory symptoms			
Dry cough	60 (76.9)	52 (66.7)	.155
Productive cough	19 (24.4)	15 (19.2)	.438
Dyspnea	46 (59.0)	29 (37.2)	<b>.006</b>
Nasal congestion	1 (1.3)	1 (1.3)	1.000*
Rhinorrhoea	1 (1.3)	2 (2.6)	1.000*
Pharyngalgia	5 (6.4)	2 (2.6)	.442*
Chest tightness	19 (24.4)	15 (19.2)	.438
Chest pain	1 (1.3)	1 (1.3)	1.000*
Gastrointestinal symptoms			
Anorexia	6 (7.7)	9 (11.5)	.415
Nausea	0 (0)	2 (2.6)	.497*
Vomiting	1 (1.3)	1 (1.3)	1.000*
Diarrhea	3 (3.8)	5 (6.4)	.719*
Abdominal distention	1 (1.3)	1 (1.3)	1.000*
Abdominal pain	1 (1.3)	1 (1.3)	1.000*
Vital signs, median (IQR)			
HR, beats per min	87.0 (79.8–98.0)	82.5 (77.8–94.0)	.081
SBP, mmHg	132.0 (122.0–140.0)	130.0 (118.8–137.3)	.276
DBP, mmHg	82.0 (72.0–88.0)	78.0 (71.0–86.0)	.272
RR, breaths per min	20.0 (20.0–20.0)	20.0 (20.0–21.0)	.253
Temp, °C	36.5 (36.5–36.6)	36.5 (36.2–36.8)	.206
Max. HR, beats per min	107.5 (98.0–115.0)	102.0 (98.0–112.0)	.087
Max. RR, breaths per min	23.0 (22.0–27.0)	22.5 (22.0–26.0)	.216
Max. Temp, °C	37.1 (36.9–37.5)	37.1 (36.9–37.4)	.811
Radiologic characteristics, median (IQR)			
Infection volume, cm <sup>3</sup>	230.7 (51.8–562.6)	353.0 (94.3–628.6)	.355
Infection proportion, %	5.8 (1.4–21.8)	11.6 (2.2–16.9)	.426

\* Compared by Fisher's exact test.

AF = atrial fibrillation, CHD = coronary heart disease, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CVD = cerebrovascular disease, DBP = diastolic blood pressure, HR = heart rate, Max. = maximum, RR = respiratory rate, SBP = systolic blood pressure, Temp. = temperature.

reflecting infection or multiple organ injury (all  $P > .05$ ) was observed between the two groups.

### 3.4. Complications and treatments

Compared with those without COPD, patients with COPD had a significant higher likelihood of progressing to respiratory failure

(19.2% vs 5.1%;  $P < .01$ ), and a marginally significant higher likelihood of developing cardiac insufficiency (10.3% vs 2.6%;  $P = .050$ ) (Table 3). With regard to treatments, patients with pre-existing COPD more likely required mechanical ventilation (16.7% vs 6.4%;  $P < .05$ ) than their non-COPD counterparts. For symptomatic treatment, these patients were more often treated with sedatives and analgesics (10.3% vs 2.6%;  $P = .050$ ),

**Table 2**  
**Laboratory tests of matched COVID-19 patients with and without COPD.**

	Patients with COPD (n = 78)	Patients without COPD (n = 78)	P
Initial laboratory examination (normal range), median (IQR)			
Infection-related indices			
IL-6, pg/mL (<7)	4.3 (1.8–13.3)	2.9 (1.5–7.7)	.249
CRP, mg/L (0–4)	5.6 (1.4–30.4)	4.9 (1.3–28.6)	.518
PCT, ng/mL (0–0.05)	0.05 (0.04–0.11)	0.05 (0.03–0.07)	.312
WBC, $\times 10^9/L$ (3.5–9.5)	6.3 (4.7–7.7)	5.7 (4.6–7.1)	.252
NEU, $\times 10^9/L$ (1.8–6.3)	3.9 (2.9–5.3)	3.7 (2.8–5.1)	.584
LYM, $\times 10^9/L$ (1.1–3.2)	1.3 (0.8–2.0)	1.2 (0.8–1.6)	.227
NLR, (1.8–5.7)	2.7 (1.9–5.0)	2.7 (2.1–5.6)	.625
Blood routine test			
RBC, $\times 10^{12}/L$ (3.8–5.1)	3.9 (3.5–4.3)	3.9 (3.5–4.3)	.972
Hb, g/L (115–150)	124.0 (109.0–134.0)	121.0 (104.8–131.3)	.329
PLT, $\times 10^9/L$ (125–350)	221.0 (164.0–272.0)	211.0 (161.8–262.0)	.654
Coagulation function test			
FIB, g/L (1.8–3.5)	3.1 (2.8–3.7)	3.2 (2.8–3.6)	.749
APTT, s (21–37)	29.0 (26.7–30.6)	29.3 (27.15–32.5)	.426
PT, s (9.2–15)	13.2 (12.3–14.0)	13.1 (12.4–14.4)	.571
TT, s (14–21)	15.4 (14.5–16.5)	15.5 (14.6–16.3)	.478
INR, (0.8–1.25)	1.1 (1.0–1.2)	1.1 (1.1–1.2)	.772
D-Dimer, mg/L (0–0.55)	1.0 (0.4–2.0)	0.9 (0.5–1.5)	.411
PTA, (70–125)	93.4 (89.3–98.2)	94.1 (88.1–98.0)	.804
Myocardial injury markers			
CKMB, IU/L (0–24)	9.9 (7.6–12.4)	8.9 (7.5–12.2)	.531
LDH, IU/L (120–250)	202.1 (165.2–246.5)	182.8 (155.5–234.9)	.163
$\alpha$ -HBDH, IU/L (72–182)	168.9 (134.3–198.4)	154.8 (127.1–194.2)	.273
MYO, ng/mL (0–65)	11.2 (6.3–22.4)	8.9 (5.3–20.5)	.354
cTnl, ng/mL (0–0.04)	0.01 (0.01–0.02)	0.01 (0.01–0.02)	.510
BNP, pg/mL (0–100)	25.9 (0.0–109.5)	36.7 (0.0–116.3)	.749
Liver function indices			
ALT, IU/L (7–40)	18.0 (11.9–27.5)	21.4 (13.1–35.9)	.221
AST, IU/L (7–45)	19.2 (15.6–26.1)	20.8 (16.2–25.8)	.764
TB, g/L (20–30)	63.6 (58.6–67.7)	60.2 (57.4–65.5)	.064
ALB, g/L (40–55)	35.6 (32.3–38.4)	35.3 (31.9–37.4)	.400
TBIL, $\mu\text{mol}/L$ (0–21)	10.0 (7.4–12.7)	10.1 (8.2–13.7)	.585
DBIL, $\mu\text{mol}/L$ (0–8)	3.7 (2.7–4.7)	3.6 (2.6–4.9)	.800
$\gamma$ -GT, IU/L (7–45)	31.2 (21.6–46.3)	25.0 (18.2–40.8)	.178
Kidney function indices			
BUN, mmol/L (3.1–8.8)	5.0 (4.0–6.5)	5.0 (3.9–6.0)	.346
Cr, $\mu\text{mol}/L$ (41–81)	69.0 (60.7–81.3)	69.8 (57.6–81.3)	.826
CysC, mg/L (22–29)	1.1 (0.9–1.3)	1.1 (0.9–1.2)	.401
Electrolytes and glucose			
CO <sub>2</sub> , mmol/L (22–29)	25.0 (22.8–27.0)	24.7 (23.0–25.9)	.309
Na <sup>+</sup> , mmol/L (137–147)	140.9 (138.7–143.0)	140.6 (138.8–142.4)	.596
K <sup>+</sup> , mmol/L (3.5–5.3)	4.3 (4.0–4.6)	4.2 (3.9–4.6)	.393
Ca <sup>2+</sup> , mmol/L (2.11–2.52)	2.1 (2.0–2.2)	2.1 (2.0–2.2)	.072
Cl <sup>-</sup> , mmol/L (99–110)	105.1 (102.2–107.2)	105.5 (103.8–107.4)	.283
Glu, mmol/L (3.9–6.1)	4.9 (4.5–5.7)	5.0 (4.6–5.8)	.371
Peak/lowest value during hospitalization (normal range), median (IQR)			
Max. IL-6, pg/mL (<7)	5.6 (2.6–29.9)	3.0 (1.5–7.7)	.017
Max. CRP, mg/L (0–4)	10.5 (2.4–57.8)	5.6 (1.8–37.6)	.294
Max. PCT, ng/mL (0–0.05)	0.05 (0.04–0.16)	0.05 (0.03–0.10)	.208
Min. Hb, g/L (115–150)	118.0 (102.0–130.0)	114.0 (99.5–127.5)	.285
Max. WBC, $\times 10^9/L$ (3.5–9.5)	7.2 (5.6–10.1)	6.7 (4.9–8.4)	.041
Min. PLT, $\times 10^9/L$ (125–350)	198.0 (130.0–234.5)	184.0 (150.0–235.5)	.768
Min. FIB, g/L (1.8–3.5)	2.9 (2.5–3.2)	2.9 (2.5–3.3)	.583
Max. PT, s (9.2–15)	13.4 (12.6–14.7)	13.2 (12.6–14.5)	.690
Max. TT, s (14–21)	15.8 (14.9–17.1)	15.8 (15.1–16.9)	.943
Max. INR, (0.8–1.25)	1.1 (1.1–1.2)	1.1 (1.1–1.2)	.539
Max. D-Dimer, mg/L (0–0.55)	1.2 (0.5–2.7)	1.0 (0.5–2.3)	.512
Min. PTA, (70–125)	92.2 (85.9–96.9)	94.1 (88.0–97.6)	.433
Max. CKMB, IU/L (0–24)	11.4 (8.4–16.3)	10.1 (7.7–14.7)	.119
Max. cTnl, ng/mL (0–0.04)	0.01 (0.01–0.02)	0.01 (0.01–0.02)	.510
Max. BNP, pg/mL (0–100)	46.9 (10.3–174.2)	48.8 (0.0–198.4)	.992
Max. ALT, IU/L (7–40)	23.9 (13.9–42.6)	23.8 (14.8–43.6)	.807
Max. AST, IU/L (7–45)	23.1 (17.1–36.4)	24.0 (18.1–30.9)	.958
Min. ALB, g/L (40–55)	34.5 (29.6–38.3)	34.5 (31.5–36.8)	.777
Max. TBIL, $\mu\text{mol}/L$ (0–21)	10.2 (8.0–14.2)	10.4 (8.5–13.7)	.800
Max. Cr, $\mu\text{mol}/L$ (41–81)	73.6 (61.9–84.9)	72.8 (61.6–83.8)	.757

ALB = albumin, ALT = alanine transaminase, APTT = activated partial thromboplastin time, AST = aspartate transaminase, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, CKMB = creatine kinase MB, COPD = chronic pulmonary obstructive disease, Cr = creatinine, CRP = C-reactive protein, cTnl = cardiac troponin I, CysC = cystatin C, DBIL = direct bilirubin, FIB = fibrinogen, Glu = glucose, Hb = hemoglobin, IL-6 = interleukin-6, INR = international normalized ratio, LDH = lactate dehydrogenase, LYM = lymphocyte, MYO = myoglobin, NEU = neutrophil, NLR = neutrophil-to-lymphocyte ratio, PCT = procalcitonin, PLT = blood platelet, PT = prothrombin time, PTA = prothrombin activity, RBC = red blood cell, TBIL = total bilirubin, TT = thrombin time, WBC = white blood cell.

**Table 3**  
**Complications and outcomes of matched COVID-19 patients with and without COPD.**

	Patients with COPD (n = 78)	Patients without COPD (n = 78)	P*
Complications, No. (%)			
Cardiac injury	13 (16.7)	7 (9.0)	.151
Cardiac insufficiency	8 (10.3)	2 (2.6)	<b>.050</b>
Acute liver injury	7 (9.0)	2 (2.6)	.167*
Hypoproteinemia	7 (9.0)	1 (1.3)	.063*
Anemia	35 (44.9)	44 (56.4)	.106
AKI	16 (20.5)	12 (15.4)	.404
SIC	15 (19.2)	14 (17.9)	.837
DIC	5 (6.4)	3 (3.8)	.719*
ARDS	6 (7.7)	2 (2.6)	.276*
Respiratory failure	15 (19.2)	4 (5.1)	<b>.007</b>
Hepatic failure	1 (1.3)	1 (1.3)	1.000*
Kidney failure	3 (3.8)	1 (1.3)	.620*
MODS	4 (5.1)	3 (3.8)	1.000*
Septic shock	5 (6.4)	1 (1.3)	.210*
Outcomes, No. (%)			
Length of stay, median (IQR), d	13.5 (8.0–18.3)	14.0 (8.0–21.3)	.740
Disease progression	45 (57.7)	36 (46.2)	.149
Disease deterioration	20 (25.6)	9 (11.5)	<b>.024</b>
Composite endpoint	16 (20.5)	5 (6.4)	<b>.010</b>
Death	8 (10.3)	2 (2.6)	<b>.050</b>
Onset of symptom to, median (IQR), d			
Disease progression	31.5 (15.0–49.3)	31.0 (18.0–44.0)	.975
Disease deterioration	41.0 (21.0–54.0)	39.0 (30.0–51.0)	.734
Discharge	50.0 (31.8–59.3)	40.0 (32.0–53.3)	.166
Composite endpoint	46.0 (26.0–55.3)	40.0 (31.0–52.3)	.861

\* Compared by Fisher's exact test.

AKI = acute kidney injury, ARDS = acute respiratory distress syndrome, COPD = chronic pulmonary obstructive disease, DIC = disseminated intravascular coagulation, GIB = gastrointestinal bleeding, MODS = multiple organ dysfunction syndrome, SIC = sepsis-induced coagulopathy.

beta-blockers (32.1% vs 17.9%;  $P = .040$ ) and antianginal drugs (25.6% vs 11.5%;  $P = .020$ ) for treating discomfort, tachycardia and symptoms of myocardial ischemia, respectively. Although more likely representing dyspnea upon admission, the use of anti-asthmatic agents was not more frequently used in patients with COPD. Instead, greater proportions of COPD patients required expectorants than their non-COPD counterparts (Table 4).

### 3.5. Outcomes

As shown in Table 3, patients with COPD more likely experienced disease deterioration (25.6% vs 11.5%;  $P = .024$ ) instead of disease progression (57.7% vs 46.2%;  $P = .149$ ). Despite no significant difference seen in the length of stay ( $P = .740$ ) between the two groups, those with COPD had worse clinical outcomes (20.5% vs 6.4%;  $P = .010$ ), with marginally significant higher rate of death (10.3% vs 2.6%;  $P = .050$ ). Kaplan–Meier survival curve also indicated that although pre-existing COPD did not influence the risk of disease progression (hazard ratio [HR], 1.227; 95% CI, 0.789–1.908;  $P = .363$ ), it increased the risk of disease deterioration by 139.4% (HR, 2.394; 95% CI, 1.088–5.265;  $P = .025$ ) and the risk of unfavorable clinical outcomes by 230.8% (HR, 3.308; 95% CI, 1.210–9.043;  $P = .013$ ) in patients with COVID-19. In addition, there was a trending increase in the risk of mortality in those with COPD compared with their non-COPD counterparts (HR, 3.875; 95% CI, 0.821–18.297;  $P = .065$ ) (Fig. 2A–D). Finally, viral clearance was determined *via* PCR test for SARS-

CoV-2 in upper respiratory tract specimens. Surprisingly, we observed that the median time from symptom onset to negative PCR result was significantly longer in COVID-19 patients with COPD compared to their non-COPD counterparts (39.0 [30.4–47.6] vs 29.0 [26.0–32.0] days;  $P = .006$ ) (Fig. 2E).

Initial univariable Cox regression analyses of demographic variables identified COPD as a risk factor (HR, 3.768; 95% CI, 1.306–10.872;  $P = .014$ ) for adverse clinical outcomes. Subsequently, a multivariable model conducted with a forward stepwise approach, which incorporated age, COPD, and CHD, showed that COPD was an independent predictor (HR, 3.915; 95% CI, 1.337–11.463;  $P = .013$ ) for unfavorable outcome of COVID-19 (Table 5).

## 4. Discussion

This study touched the clinical characteristics of COVID-19 patients with COPD in comparison to sex- and age-matched COVID-19 patients without COPD. COPD was identified as an independent risk factor of unfavorable outcomes of COVID-19. Among COVID-19 patients hospitalized in Wuhan Huoshenshan Hospital from February 5 to March 15, 2020, the prevalence of COPD was 2.6% (78/2994). In comparison with their non-COPD counterparts, patients with COPD more likely suffered respiratory failure and cardiac insufficiency, had disease deterioration, and yielded worse clinical outcomes. However, those with COPD did not show a propensity for over-activated inflammation status and subsequent multi-organ injury.

**Table 4**  
**Treatment of matched COVID-19 patients with and without COPD.**

Treatments, No. (%)	Patients with COPD (n=78)	Patients without COPD (n=78)	P*
Oxygen therapy			
Oxygen inhalation	70 (89.7)	72 (92.3)	.575
High-flow nasal cannula	9 (11.5)	4 (5.1)	.148
Mechanical ventilation	13 (16.7)	5 (6.4)	<b>.045</b>
Non-invasive	11 (14.1)	3 (3.8)	
Invasive	7 (9.0)	2 (2.6)	
Renal replacement therapy	4 (5.1)	1 (1.3)	.367*
Bronchoalveolar lavage	1 (1.3)	1 (1.3)	1.000*
Antivirals	43 (55.1)	39 (50.0)	.521
Umidenovir	38 (48.7)	33 (42.3)	
Oseltamivir	5 (6.4)	9 (11.5)	
Ribavirin	4 (5.1)	3 (3.8)	
Interferon	4 (5.1)	12 (15.4)	
Chloroquine	3 (3.8)	2 (2.6)	
Antibacterials			
First and second-line antibacterials	37 (47.4)	33 (42.3)	.520
Quinolones	32 (41.0)	30 (38.5)	
Cephalosporins	5 (6.4)	8 (10.3)	
Macrolides	3 (3.8)	0 (0)	
Third-line antibacterials	19 (24.4)	12 (15.4)	.160
Cephalosporins	0 (0)	1 (1.3)	
β-lactamase inhibitors	17 (21.8)	10 (12.8)	
Carbapenems	8 (10.3)	3 (3.8)	
Vancomycin	0 (0)	1 (1.3)	
Tigecycline	1 (1.3)	0 (0)	
Linezolid	5 (6.4)	4 (5.1)	
Antifungals	6 (7.7)	5 (6.4)	.754
Immunomodulators			
Glucocorticoids	29 (37.2)	21 (26.9)	.170
Immunoglobulin	5 (6.4)	7 (9.0)	.548
Thymosin	23 (29.5)	23 (29.5)	1.000
Tocilizumab	8 (10.3)	4 (5.1)	.229
Convalescent plasma	6 (7.7)	8 (10.3)	.575
Mesenchymal stem cell therapy	6 (7.7)	3 (3.8)	.495*
Drugs for cardiovascular disorders			
Cardiotonic drugs	8 (10.3)	5 (6.4)	.385
Beta-blockers	25 (32.1)	14 (17.9)	<b>.042</b>
Amiodarone	4 (5.1)	0 (0)	.120*
Antianginal drugs	20 (25.6)	9 (11.5)	<b>.024</b>
Creatine phosphate	2 (2.6)	2 (2.6)	1.000*
Antilipemic agents	9 (11.5)	12 (15.4)	.482
Anticoagulants	12 (15.4)	16 (20.5)	.404
Drugs for gastrointestinal disorders			
Acid inhibitors	33 (42.3)	27 (34.6)	.323
Laxatives	15 (19.2)	23 (29.5)	0.136
Antidiarrheics	6 (7.7)	7 (9.0)	1.000
Gastrointestinal stimulants	13 (16.7)	7 (9.0)	.151
Probiotics	21 (26.9)	28 (35.9)	.227
Hepatic protectants	7 (9.0)	13 (16.7)	.151
Drugs for respiratory disorders			
Anti-asthmatics	43 (55.1)	34 (43.6)	.150
Expectorants	46 (59.0)	28 (35.9)	<b>.004</b>
NSAIDs	15 (19.2)	12 (15.4)	.525
Sedatives & analgesics	8 (10.3)	2 (2.6)	<b>.050</b>

\* Compared by Fisher's exact test.

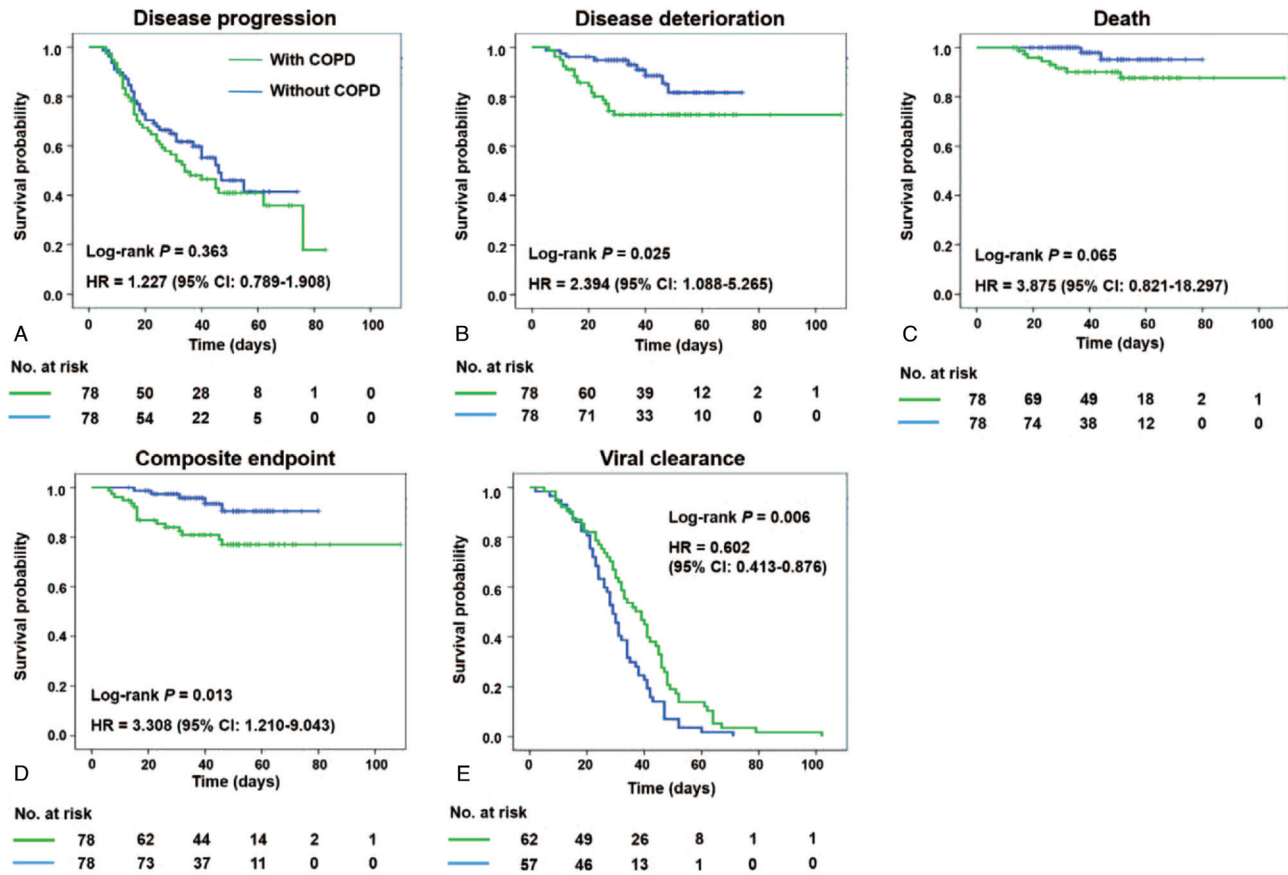
COPD=chronic pulmonary obstructive disease, NSAID=nonsteroidal anti-inflammatory drug.

Dyspnea is a common symptom in COVID-19 patients, especially in severe cases.<sup>[32]</sup> It is caused by the damage of lung tissue and exudation of pulmonary edema fluid owing to the over-activated immunoreaction during SARS-CoV-2 infec-

tion.<sup>[33]</sup> Apart from pulmonary causes, the nervous system is also implicated in the development of dyspnea. The dyspnea neurocircuitry includes proprioceptive and broncho-pulmonary afferents and centrally generated inspiratory motor output, with the sensorimotor cortex, limbic system, and brainstem respiratory center involved.<sup>[34,35]</sup> In our prior study, we have noticed that a lower proportion of COVID-19 patients with pre-existing cerebrovascular disease (CVD) presented with dyspnea at disease onset compared with those without CVD, which possibly resulted from the dysfunction of brain areas involved in dyspnea modulation owing to ischemic or hemorrhagic stroke.<sup>[16]</sup> However, for COPD, pulmonary causes instead of neural mechanisms play a key role in dyspnea. COPD pathophysiology is characterized by chronic bronchitis and emphysema. The former leads to airway wall thickness, mucus hypersecretion, and narrowed bronchioles, while the latter induces the destruction of alveoli structure.<sup>[36]</sup> Herein, we observed that a higher portion of COVID-19 patients with COPD presented with dyspnea at disease onset compared with their non-COPD counterparts. One reason is that a small proportion of the 78 COPD patients were at acute attack phase. Thus, the frequently seen dyspnea in this population may reflect COPD pathophysiology itself. Another explanation is that COPD pathophysiology and COVID-19 pathophysiology may exert synergistic effects that lead to pulmonary over-inflammation and functional collapse, which eventually lead to dyspnea and respiratory failure.

In the present study, we observed that although COVID-19 patients with COPD did not show a propensity for disease progression, COPD conferred a higher risk for disease deterioration and unfavorable clinical outcomes, which was consistent with previous studies.<sup>[8,9,11,12]</sup> COPD usually occurs in later life with high prevalence of associated comorbidities. In addition, COPD itself was characterized by lung dysfunction and immune dysregulation of the airways. All these features were considered to account for worse outcomes in COVID-19 patients with pre-existing COPD.<sup>[37-39]</sup> Herein, we observed that those with COPD more likely presented dyspnea, developed respiratory failure and cardiac insufficiency, and necessitated more expectorants, anti-bradycardia drugs, and mechanical ventilation than their non-COPD counterparts, suggesting the occurrence of acute exacerbation of COPD (AECOPD) in these patients. Viral or bacterial infection is the major etiological trigger for AECOPD. This kind of AECOPD, characterized by more marked impairment in pulmonary function, was severer than those with non-infectious causes (such as pulmonary embolism, smoking, and heart failure).<sup>[40]</sup> Considering these, we postulated that COVID-19-triggered AECOPD and subsequent respiratory failure were the main culprit for mortality among these patients.

Cell entry of SARS-CoV-2 through angiotensin-converting enzyme 2 (ACE2),<sup>[41]</sup> causes limited damage to the lung and other target organs in most cases owing to virus clearance from the respiratory system *via* adaptive immune reactions.<sup>[42]</sup> However, aberrant uncontrolled response, also known as “cytokine storm,” could lead to ARDS, MODS, and even death in severe cases.<sup>[43,44]</sup> Herein, clinical evidence from imaging data, laboratory tests, complications, and therapeutics did not reveal the existence of severer lung infection, cytokine storm and subsequent multi-organ injury in COVID-19 patients with COPD. This seems to contradict with prior studies by Alberca et al and He et al concluding that COVID-19 patients with COPD had severer infection and inflammatory responses.<sup>[8,11]</sup>



**Figure 2.** Kaplan–Meier plots for different clinical outcomes in patients with and without chronic obstructive pulmonary disease. The figure displays the Kaplan–Meier survival plots according to disease progression (A), disease deterioration (B), death (C), composite endpoint (D), and viral clearance (E). COPD=chronic obstructive pulmonary disease, HR=hazard ratio.

These authors believed that the up-regulation of ACE2 in COVID-19 patients with COPD was esteemed to confer a higher level of COVID-19 severity.<sup>[45]</sup> However, this hypothesis was challenged by the fact that the elderly, a high-risk population for severe COVID-19, exhibited a lower level of ACE2 in the lungs.<sup>[38,46]</sup> Additionally, the relatively lower expression of ACE2 within the bronchial epithelium compared with the nasal epithelium could not account for predominantly small airways pathology of COVID-19.<sup>[47]</sup> In light of these, the up-regulated

expression of ACE2 in patients with COPD may not be enough to explain the increased disease severity.

The possible explanation for this discrepancy is that our study design differs from those of prior studies by Alberca et al and He et al.<sup>[8,11]</sup> A matching method was used in the present study to control the impact of discrepancy in demographical features on COVID-19, since the objective of our study was to examine the influence of the pathophysiology of COPD on the clinical course of COVID-19. Apart from the risk conferred by age and sex,

**Table 5**  
**Cox regression analyses of risk factors for outcome for composite endpoint of matched COVID-19 patients with and without COPD.**

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, y	1.042 (1.000–1.085)	.048	1.044 (1.001–1.088)	.043
Male	1.789 (0.567–5.652)	.321		
Hypertension	1.994 (0.790–5.003)	.144		
Diabetes	2.500 (0.801–7.806)	.115		
CHD	2.435 (0.885–6.699)	.085	–	–
CVD	1.750 (0.129–23.703)	.674		
COPD	3.768 (1.306–10.872)	.014	3.915 (1.337–11.463)	.013
Malignancy	1.671 (0.330–8.467)	.535		

The multivariable model contains age, CHD, and COPD.

CHD=coronary heart disease, CKD=chronic kidney disease, COPD=chronic obstructive pulmonary disease, CVD=cerebrovascular disease, HR=hazard ratio.



COPD itself was correlated with worse clinical outcomes of COVID-19. Older age has been demonstrated to be an independent risk factor of adverse outcomes in patients with COVID-19.<sup>[15]</sup> Apart from age-dependent impairment in adaptive immune function,<sup>[48]</sup> age-related comorbidities (hypertension, diabetes, CHD, etc) reflect a state of endothelial dysfunction, rendering patients more vulnerable to multi-organ hemorrhagic and ischemic complications, especially in the lungs, kidney, brain, and heart, in the end-stage of COVID-19. Considering these, we suggest that the severer infection and immune response reported by Alberca et al and He et al was owing to the older age and more comorbidities in COVID-19 patients with COPD. COPD pathophysiology itself confers increased risk of unfavorable clinical outcomes in patients with COVID-19 mainly by dysregulation of the anti-viral immune response, and their susceptibility to virus-induced exacerbations and subsequent respiratory failure.

Our study has several potential limitations. First, it was a single-center based study with a small number of cases, rendering it difficult to assess various risk factors accurately *via* multivariable regression model. Second, the findings could not be generalized to other regions around the world with differing epidemiological features, since all study participants were from the epicenter Wuhan during the early time of disease outbreak. Third, the available data failed to deal with the heterogeneity of COPD, including disease severity and exacerbation frequency, and further studies with a larger cohort on a nationwide basis should incorporate these additional susceptibility factors. Fourth, long-term follow-up of this subpopulation with COVID-19 are urgently necessitated. Despite these shortcomings, these data will provide guidance for physicians to gain a better understanding of the panorama of this disease and are beneficial to the treatment of patients with pre-existing COPD who are at high risk for severe COVID-19.

## 5. Conclusions

This study demonstrates that compared to age- and sex-matched patients without COPD, those with COPD more likely presented acute exacerbations of COPD, developed respiratory failure, and yielded poor clinical outcomes. It is also worth noting that over-activated inflammatory responses as seen in severe COVID-19 cases may not be related to the poor outcomes of COVID-19 patients with COPD.

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## Author contributions

G Liang, Y Kou, and E Wang conceived the idea, designed, and supervised the study, and had full access to all the data and took responsibility for the integrity of the data. Y Bai, L Wen, and Y Zhao analyzed data and performed statistical analysis. All the authors reviewed and approved the final version of the manuscript.

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