

Clinical Characteristics and Prognosis of COPD Patients Hospitalized with SARS-CoV-2

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Objective: To describe the characteristics and prognosis of patients with COPD admitted to the hospital due to SARS-CoV-2 infection.

Methods: The SEMI-COVID registry is an ongoing retrospective cohort comprising consecutive COVID-19 patients hospitalized in Spain since the beginning of the pandemic in March 2020. Data on demographics, clinical characteristics, comorbidities, laboratory tests, radiology, treatment, and progress are collected. Patients with COPD were selected and compared to patients without COPD. Factors associated with a poor prognosis were analyzed.

Results: Of the 10,420 patients included in the SEMI-COVID registry as of May 21, 2020, 746 (7.16%) had a diagnosis of COPD. Patients with COPD are older than those without COPD (77 years vs 68 years) and more frequently male. They have more comorbidities (hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, heart failure, ischemic heart disease, peripheral vascular disease, kidney failure) and a higher Charlson Comorbidity Index (2 vs 1, $p<0.001$). The mortality rate in COPD patients was 38.3% compared to 19.2% in patients without COPD ($p<0.001$). Male sex, a history of hypertension, heart failure, moderate-severe chronic kidney disease, presence of cerebrovascular disease with sequelae, degenerative neurological disease, dementia, functional dependence, and a higher Charlson Comorbidity Index have been associated with increased mortality due to COVID-19 in COPD patients. Survival was higher among patients with COPD who were treated with hydroxychloroquine (87.1% vs 74.9%, $p<0.001$) and with macrolides (57.9% vs 50%, $p<0.037$). Neither prone positioning nor non-invasive mechanical ventilation, high-flow nasal cannula, or invasive mechanical ventilation were associated with a better prognosis.

Conclusion: COPD patients admitted to the hospital with SARS-CoV-2 infection have more severe disease and a worse prognosis than non-COPD patients.

Keywords: SARS-CoV-2, coronavirus, COVID-19, COPD

Introduction

In December 2019, cases of pneumonia caused by a new strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were described in Wuhan, China. This was the origin of the COVID-19 pandemic declared by the World Health Organization (WHO).

Chronic obstructive pulmonary disease (COPD) is defined as the presence of persistent respiratory symptoms and limitation of air flow due to abnormalities of the airway and/or alveolar airways. It is often caused by significant exposure to harmful particles and gases. It is known that these patients have high comorbidity and that a hospital admission implies a deterioration in their quality of life and greater morbidity and mortality.^{1,2}

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Comorbidities are considered risk factors for SARS-CoV-2 infection and are associated with greater severity of the disease and a worse prognosis. Patients with COPD have been classified as an at-risk population.^{3,4}

SARS-CoV-2 spike (S) protein binds angiotensin converting enzyme 2 (ACE2) and together with host transmembrane serine protease 2 (TMPRSS2) promotes cell entry. The expression of ACE2 and TMPRSS2 has been identified in lung type II pneumocytes, ileal absorptive enterocytes, and nasal goblet secretory cells. Increased expression of genes related to ACE2 and CD147 has been described in asthma, COPD, hypertension, smoking, obesity, and male gender status. This may predispose individuals to an increased risk of coronavirus respiratory tract infections in active smokers and virus-related exacerbations in patients with COPD.^{5–7}

In mice, ACE2 and angiotensin II receptor type 2 (AT2) have been shown to protect them from severe acute lung injury induced by acid aspiration or sepsis, whereas ACE, angiotensin II and the angiotensin II type 1a receptor (AT1a) induces lung oedema and impair lung function. The same authors show that ACE-deficient mice show milder disease and that recombinant ACE2 can protect them from severe acute lung injury.⁸

The altered expression of these receptors could contribute to the patterns of morbidity and severity of COVID-19.

Two reviews have been published on this issue. In the first review, which is one of 11 general case series that aim to assess the prevalence of severe COVID-19 in patients with COPD who are smokers, concluded that COPD and a history of active smoking implied a worse prognosis.⁹ In the second review regarding COPD patients with COVID-19, the risk of severe disease (63%) and mortality (60%) was high, indicating that these patients have an increased risk of serious complications and death.¹⁰

In order to better manage patients with COPD who require hospitalization due to SARS-CoV-2 infection, we must know the predisposing factors, observe the clinical presentation, provide guidelines on appropriate treatment, and monitor their progress and prognosis in order to provide them with the best therapeutic management.

In Spain, at least half of COPD patients are hospitalized in internal medicine departments. Furthermore, the majority of patients hospitalized for SARS-CoV-2 are cared for in internal medicine units. This makes the collection of information from these departments feasible.¹¹

The aim of this work is to analyze the characteristics and prognosis of COPD patients admitted to the hospital due to SARS-CoV-2 infection.

Materials and Methods

Observational Study

The SEMI-COVID-19 registry is an ongoing retrospective cohort comprising consecutive patients hospitalized in 150 hospitals in Spain from March 2020 with confirmed COVID-19 disease who died during hospitalization or were discharged.¹² Inclusion began on March 27 and is still ongoing. A complete list of the SEMI-COVID-19 Network members is provided in the [Appendix](#).

All consecutive patients with confirmed SARS-CoV-2 infection who were discharged after hospitalization or who died were eligible for inclusion in the registry. COVID-19 disease was confirmed either by a positive result on real-time polymerase chain reaction (RT-PCR) testing of a nasopharyngeal or sputum sample or by a positive result on serological testing and a clinically compatible presentation. Inclusion criteria for the registry were: a) patient age ≥ 18 years, b) a confirmed diagnosis of COVID-19, c) first hospital admission in a Spanish hospital participating in the registry, d) hospital discharge or in-hospital death.

Patients were treated at their attending physician's discretion, according to local protocols and clinical judgment.

The data is retrospectively collected from medical records by clinical researchers from across the country. Data are collected on almost 300 variables, grouped into several sections: (1) inclusion criteria; (2) epidemiological data; (3) RT-PCR and serology; (4) personal history and previous medication; (5) symptoms and physical examination upon admission; (6) laboratory tests (arterial blood gas, biochemical analysis, complete blood count, coagulation) and imaging on admission; (7) additional data seven days after admission or admission to an intensive care unit; (8) pharmacological treatment during admission (antivirals, immunomodulators, antibiotics) and ventilatory support; (9) complications during hospitalization, and (10) evolution after discharge and/or 30 days after diagnosis. The variables in the registry have been described previously.¹²

An online electronic data capture system (DCS) has been developed. The DCS includes a database administrator and a set of procedures for data verification. Patients are de-identified in the registry, identifiable data are dissociated and pseudonymised using an alphanumeric code.

Each investigator maintains a protected patient registry in order to verify data and control quality. The database platform is hosted on a secure server, both the database and each client-server transfer being encrypted. The pseudonymisation system allows patient privacy to be respected while complying with ethical considerations and data protection regulations.

The Spanish Society of Internal Medicine (SEMI) is the promoter of this study. The investigators who coordinate the study in each hospital are partners of SEMI and agreed to participate in the study voluntarily and without any remuneration. The monitoring of the study is carried out by the scientific committee of the same and an independent agency. Logistical coordination and data analysis are also carried out by independent agencies.

For this work, the patients included in the SEMI-COVID-19 Registry who had the diagnosis of COPD recorded in their medical history as a personal history were selected, without the obligation to have a diagnostic spirometry. In those who had a spirometry reflected in their clinical history, the percentage value of FEV1 was collected.

The variables selected for analysis included demographic variables (age, sex, obesity, smoking, comorbidities, degree of dependence and use of inhaled or oral corticosteroids, antivitamin K drugs, antiplatelets, statins, ACE inhibitors, Angiotensin-renin blockers); clinical variables on admission (signs and symptoms, laboratory results and radiological findings); treatment received on admission (beta-lactams, macrolides, quinolones, hydroxychloroquine, lopinavir/ritonavir, remdesivir, systemic corticosteroids, immunoglobulins, beta interferon, tocilizumab or anakinra); radiological evolution, ventilatory support (invasive and non-invasive mechanical ventilation and high-flow oxygen therapy) and clinical results (admission to the ICU and death).

Data on patients with COPD were selected and compared to data on non-COPD patents. Factors indicating poor prognosis were analyzed, defined as all-cause mortality. All-cause mortality during hospitalization was the primary endpoint.

For the subsequent data analysis, the STATA statistical system was used.

Qualitative variables are expressed as absolute frequency (n) and percentage (%). Quantitative variables are expressed as median, interquartile range, and range with a 95% confidence interval. Qualitative variables were compared using the chi-square test. Continuous variables

were compared using the Mann–Whitney test and logistic regression of variables. Statistical significance was defined as a p value <0.05.

Ethical Aspects

Personal data is processed in strict compliance with Law 14/2007, of July 3, on Biomedical Research; Regulation (EU) 2016/679 of the European Parliament and of the Council, of April 27, 2016, on the protection of natural persons with regard to the processing of personal data and the free circulation of said data, and by which repeals Directive 95/46/EC (General Data Protection Regulation); and Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights. The SEMI-COVID-19 Registry was first approved by the Provincial Research Ethics Committee of Malaga (Spain), following the recommendation of the Spanish Agency for Medicines and Health Products (AEMPS). Informed consent was requested from the patients. When it was not possible to obtain it in writing for biosafety reasons or because the patient was already discharged from hospital, verbal informed consent was requested and entered in the medical record.

Results

Of a total of 10,420 patients included in the SEMI-COVID-19 registry as of May 21, 2020, 746 (7.16%) had a history of COPD. [Tables 1](#) and [2](#) showed the characteristics of non-COPD and COPD patients. The data indicated that COPD patients were older than patients without COPD (77 years vs 68 years) and were more likely to be male (82.2% vs 54.7%). They had more comorbidities, especially cardiovascular comorbidities (hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, heart failure, ischemic heart disease, peripheral vascular disease, renal failure); a higher Charlson Comorbidity Index and age-corrected Charlson Comorbidity Index (3 vs 6, $p<0.001$); and had greater functional dependence. FEV1 was recorded for 364 patients with COPD, with a mean FEV1 of 59%.

The percentage of patients with COPD who were treated with systemic corticosteroids was 7.4% and the percentage treated with inhaled corticosteroids was 47.2%. Patients with COPD were also more likely to have had been taking antiplatelet drugs, anticoagulants, statins, ACE inhibitors, and angiotensin-renin blockers.

In patients with COPD, the clinical presentation of COVID-19 usually involved low-grade fever, dyspnea, and expectoration, with fewer non-respiratory symptoms than non-COPD patients. On examination, these patients

Table 1 Characteristics of People with Coronavirus Disease 2019 with or without COPD. Demographic Data and Comorbidity

Characteristics	Values are Indicated as the Number (Percentage) or Median (Interquartile Range)				
	Overall (n=10,420)	N (%)	Non-COPD (n=9674)	COPD (n=746)	P value
Median (IQR) age (years)	10,385	69 (55–79)	68 (54–79)	77 (71–84)	-
Age (years):					
<45 years	10,385	1130 (10.9)	1130 (11.7)	0 (0.0)	-
45–55 years		1325 (12.8)	1316 (13.7)	9 (1.2)	<0.001
55–65 years		1884 (18.1)	1798 (18.7)	86 (11.6)	<0.001
65–75 years		2258 (21.7)	2049 (21.3)	209 (28.1)	0.596
75–85 years		2263 (21.8)	1973 (20.5)	290 (39)	0.004
>85 years		1525 (14.7)	1376 (14.3)	149 (20.0)	omitted
Men	10,401	5893 (56.7)	5281 (54.7)	612 (82.2)	<0.001
Smoking status					
Never	9904	6890 (69.6)	6783 (74)	107 (14.7)	-
Former		2482 (25.0)	1968 (21.4)	514 (70.7)	<0.001
Current		532 (5.4)	426 (4.6)	106 (14.6)	0.46
Alcohol use disorder	10,112	470 (4.7)	384 (4.0)	86 (11.8)	<0.001
Obesity (BMI>30)	4597	1537 (33.4)	1415 (33.6)	122 (32.1)	0.57
Hypertension	10,404	5242 (50.4)	4729 (48.9)	513 (69.1)	<0.001
Hyperlipidemia	10,401	4078 (39.2)	3682 (38.1)	396 (53.4)	<0.001
Diabetes Mellitus	10,379	1936 (18.7)	1745 (18.1)	191 (25.8)	<0.001
Anxiety disorder	10,377	842 (8.1)	779 (8.0)	63 (8.5)	0.71
Depression	10,376	1092 (10.5)	1014 (10.5)	78 (10.5)	0.99
Atrial fibrillation	10,395	1175 (11.3)	1000 (10.4)	175 (23.6)	<0.001
Myocardial infarction	10,410	619 (5.6)	521 (5.4)	98 (13.2)	<0.001
Heart failure	10,406	775 (7.5)	643 (6.7)	132 (17.8)	<0.001
Transient ischemic attack	10,377	747 (7.2)	657 (6.8)	90 (12.2)	<0.001
Dementia	10,403	1066 (10.3)	987 (10.2)	79 (10.6)	0.74
Neurodegenerative disease	10,401	979 (9.4)	908 (9.4)	71 (9.5)	0.89
Peripheral arterial disease	10,397	503 (4.8)	414 (4.3)	89 (12.0)	<0.001
Mild chronic liver disease	10,393	294 (2.8)	255 (2.6)	39 (5.2)	<0.001
Moderate–severe chronic liver disease	10,401	110 (1.0)	90 (0.9)	20 (2.7)	<0.001
Chronic kidney disease	10,399	631 (6.1)	549 (5.7)	82 (11.0)	<0.001
Dialysis	10,352	16 (0.2)	14 (0.2)	2 (0.3)	0.64
Cancer	10,388	845 (8.1)	740 (7.7)	105 (14.1)	<0.001
Obstructive Sleep Apnea Syndrome	10,337	654 (6.3)	524 (5.5)	130 (17.6)	<0.001
Dependency status					
Independent	10,250	8519 (83.1)	7960 (83.7)	559 (76.7)	-
Moderate dependency		984 (9.6)	856 (9.0)	128 (17.4)	<0.001
Severe dependency		747 (7.3)	700 (7.4)	47 (6.4)	0.76
Charlson Comorbidity Index	10,084	1 (0–2)	1 (0–2)	2 (1–4)	<0.001
Charlson Comorbidity Index, age corrected	10,048	3 (1–5)	3 (1–5)	6 (4–8)	<0.001

were more likely to present with hypoxemia, tachypnea, and confusional symptoms, with the presence of rhonchi and wheezing on pulmonary auscultation.

All-cause mortality in COPD patients was 38.3%, compared to 19.2% in non-COPD patients ($p<0.001$). Male sex, a history of hypertension, heart failure, moderate–severe

chronic kidney disease, the presence of cerebrovascular disease with sequelae, degenerative neurological disease, dementia, functional dependence, and a higher Charlson Comorbidity Index had been associated with higher mortality in COPD patients (Tables 3 and 4). The relationship was nearly significant in patients with a history of myocardial

Table 2 Characteristics of People with Coronavirus Disease 2019 with or without COPD. Clinical Data and Evolution

Characteristics	Values are Indicated as the Number (Percentage) or Median (Interquartile Range)				
	Overall (n=10,420)	N (%)	Non-COPD (n=9674)	COPD (n=746)	P value
Habitual treatment					
Immunosuppressants	10,383	362 (3.5)	335 (3.5)	27 (3.6)	0.82
Systemic corticosteroids	10,392	450 (4.3)	395 (4.0)	55 (7.4)	<0.001
Inhaled corticosteroids	10,340	1031 (10.0)	683 (7.1)	348 (47.2)	<0.001
Anticoagulants					
None	10,338	9148 (88.5)	8582 (89.4)	566 (76.4)	-
Antivitamin K		653 (6.3)	552 (5.8)	101 (13.6)	<0.001
DOACs		456 (4.4)	388 (4.0)	68 (9.2)	<0.001
LMWH		81 (0.8)	75 (0.8)	6 (0.8)	0.65
Antiplatelet drugs	10,319	1591 (15.4)	1393 (14.5)	198 (26.9)	<0.001
Statins	10,319	3302 (32.0)	2928 (30.6)	374 (50.6)	<0.001
ACE inhibitors	10,330	1757 (17.0)	1590 (16.6)	167 (22.6)	<0.001
Angiotensin-renin blockers	10,334	2014 (19.5)	1829 (19)	185 (25)	<0.001
Symptoms and vital signs					
Temperature >38 °C	10,369	6581 (63.5)	6181 (64.2)	400 (53.8)	<0.001
Low-grade fever	10,369	2195 (21.2)	2025 (21)	170 (22.9)	<0.001
Dyspnea	10,369	5939 (53.4)	5402 (56.2)	537 (72.3)	<0.001
Dry cough	10,368	6084 (58.7)	5724 (59.5)	360 (48.5)	<0.001
Cough with expectoration		1652 (15.9)	1452 (15.1)	200 (26.9)	<0.001
Fatigue	10,157	4493 (44.2)	4193 (44.5)	300 (41.2)	0.088
Anorexia	10,102	2045 (20.2)	1903 (20.3)	142 (19.6)	0.68
Myalgia	10,198	3146 (30.9)	2969 (31.4)	177 (24.2)	<0.001
Headache	10,160	1192 (11.7)	1152 (12.2)	40 (5.5)	<0.001
Diarrhea	10,287	2339 (22.7)	2239 (23.5)	100 (13.6)	<0.001
Nausea	10,121	1274 (12.6)	1233 (13.1)	41 (5.7)	<0.001
Vomiting	10,249	759 (7.4)	740 (7.8)	19 (2.6)	<0.001
Abdominal pain	10,235	683 (6.7)	649 (6.8)	34 (4.6)	0.022
Ageusia	9971	656 (6.6)	632 (6.8)	24 (3.4)	<0.001
Anosmia	9967	584 (5.9)	563 (6.1)	21 (3.0)	0.001
Sore throat	10,147	994 (9.8)	926 (9.8)	68 (9.4)	0.68
Vital signs at triage					
Temperature >38 °C	9978	1611 (16.2)	1516 (16.4)	95 (13.3)	0.029
Temperature, median (IQR) °C	9978	37 (36.4–37.8)	36.9 (36.2–37.7)	37 (36.4–37.8)	0.004
Sat <90%	10,084	2211 (21.9)	1928 (20.6)	283 (38.8)	<0.001
SatO2% Median (IQR)	10,084	94 (91–97)	95 (91–97)	92 (88–95)	<0.001
Respiratory rate >20 breaths/min	10,097	3145 (31.2)	2797 (29.9)	348 (47.9)	<0.001
Heart rate >100 beats/min	9990	2181 (21.8)	2036 (22.0)	145 (20.0)	0.22
Heart rate Median (IQR)	9990	87 (76–100)	87 (76–100)	85 (75–98)	0.08
SBP, median (IQR) mmHg	9870	127 (114–141)	127 (115–140)	127 (113–144)	0.96
DBP, median (IQR) mmHg	9860	74 (65–82)	74 (65–82)	72 (61–80)	<0.001
Confusion	10,270	1227 (12.0)	1100 (11.5)	127 (17.3)	<0.001
Wheezing	10,105	625 (6.2)	501 (5.3)	124 (17.3)	<0.001
Rhonchi	10,097	1088 (10.8)	890 (9.5)	198 (27.6)	<0.001
Crackles	10,107	5324 (52.7)	4937 (52.6)	387 (53.9)	0.49
Evolution					
Non-invasive mechanical ventilation	10,327	503 (4.9)	429 (4.5)	74 (10.1)	<0.001
High-flow nasal cannula	10,264	832 (8.1)	736 (7.7)	96 (13.2)	<0.001

(Continued)

Table 2 (Continued).

Characteristics	Values are Indicated as the Number (Percentage) or Median (Interquartile Range)				
	Overall (n=10,420)	N (%)	Non-COPD (n=9674)	COPD (n=746)	P value
Invasive mechanical ventilation	10,326	663 (6.4)	627 (6.5)	36 (4.9)	0.083
Prone position	10,307	1020 (9.9)	938 (9.8)	82 (11.2)	0.21
ICU admission	10,400	841 (8.1)	788 (8.2)	53 (7.1)	0.31
Hospital stay in days, median (IQR)	9 (5–14)		9 (5–14)	10 (6–16)	0.80
Mortality	2142 (20.6)		1856 (19.2)	286 (38.3)	<0.0001

infarction and obesity. Associating the comorbidities in clusters: risk factors, neurological, cardiovascular, hepatic-renal and oncological, we found that cardiovascular and hepatic-renal were associated with an increase in mortality in COPD patients with COVID. COPD patients with SARS-CoV2 infection who presented some comorbid pathology had higher mortality than those who did not have any comorbidity (Table 5).

Higher all-cause mortality was observed in patients in regular treatment with systemic corticosteroids and in patients who were anticoagulated and antiaggregated with acetylsalicylic acid, which could possibly reflect increased cardiovascular disease. However, neither chronic treatment with ACE inhibitors nor with angiotensin-renin blockers were associated with higher all-cause mortality in this population.

We found no differences in survival in COPD patients among current smokers, former smokers, and never smokers (Figure 1). A worse FEV1 value also did not correlate with mortality.

In regard to hemogram parameters, all-cause mortality was associated with higher levels of leukocytes (7180 vs 6400, $p = 0.002$), neutrophils (5125 vs 4640, $p = 0.004$), C-reactive protein (CRP) (99.2 vs 63.9, $p < 0.001$), creatinine (1.21 vs 1.0, $p = 0.001$), lactate dehydrogenase (LDH) (352 vs 270, $p < 0.001$), procalcitonin (0.2 vs 0.1, $p = 0.003$), and D-Dimer (1014 vs 695, $p = 0.002$).

Radiologically, the presence of bilateral condensation, bilateral interstitial infiltrates, and radiological worsening at one week was associated with an increased mortality rate.

In terms of treatment, 56.9% of COPD patients received treatment with lopinavir/ritonavir and 49% received systemic corticosteroids; greater survival was not observed among these patients. Survival was higher among patients with COPD who were treated with hydroxychloroquine (87.1% vs 74.9%, $p < 0.001$) and with macrolides (57.9% vs 50%, $p < 0.037$). An improved prognosis was not observed with the use of beta-lactams or quinolones.

Neither prone positioning, non-invasive mechanical ventilation, high-flow nasal cannula, or invasive mechanical ventilation were associated with a better prognosis.

Discussion

This is the first work that describes the characteristics and prognosis of COPD patients hospitalized with SARS-CoV-2 infection.

One of the most notable findings among these data is the low prevalence of COPD patients. Given that COVID-19 is a viral disease with respiratory involvement, it would be logical to expect to find a higher percentage of COPD patients. In previous works, the incidence of COPD in patients hospitalized with COVID-19 has been estimated to be 0.95%³ and the prevalence of patients with COVID-19 who had COPD has been estimated to be 2%.¹⁰ In previously published data from the SEMI-COVID-19 registry, the incidence of COPD was 7.7%.¹² The prevalence found in our registry is higher than in the New York area series (5.4%), but lower than some of the Chinese series.¹³

One of the reasons can explain the low prevalence of COVID-19 among COPD patients could be the use of drugs for respiratory disease like inhaled steroids, beta-agonists or anticholinergics, specially tiotropium.¹⁴ In the other side, glycopyrronium and formoterol have been shown to reduce cellular susceptibility to coronavirus infection in vitro. They do so by inhibiting the expression of coronavirus receptors, reducing endosomal activity, and modulating the inflammatory responses induced by it in the airway. Indeed, basic treatment for COPD patients usually includes long-acting muscarinic antagonists (LAMA) and/or long-acting β_2 -agonists (LABA).¹⁵ Based on this low prevalence, it could be said that COPD patients would not have an increased risk of contracting SARS-CoV2 infection. These data are taken from hospitalized patients, and to be able to affirm these results

Table 3 Mortality of COPD Patients with Coronavirus Disease 2019 According to Demographic Data and Antecedents

Values are Indicated as the Number (Percentage) or Median (Interquartile Range)					
Characteristics	Overall (n=746)	Survivors (n=460)	Deceased (n=286)	Odds Ratio (95% CI)	P value
Age (years)	77 (71–84)	75 (66–82)	79 (74–86)	1.06 (1.04–1.08)	<0.001
Men	612 (82.2)	365 (79.4)	247 (86.7)	1.69 (1.12–2.55)	0.012
Comorbidities					
FEV1					
<30	21 (5.8)	11 (4.9)	10 (7.3)	1.74 (0.58–5.26)	0.33
30–49	84 (23.1)	52 (22.9)	32 (23.4)	1.18 (0.52–2.69)	0.70
50–79	224 (61.5)	141 (62.1)	83 (60.6)	1.13 (0.53–2.39)	0.75
≥80	35 (9.6)	23 (10.1)	12 (8.8)	Ref. (1)	-
FEV1 <50	105 (28.8)	63 (27.8)	42 (30.7)	1 (ref.)	-
FEV1 >50	259 (71.2)	164 (72.2)	95 (69.3)	0.87 (0.55–1.38)	0.55
Smoking status					
Never	107 (14.8)	59 (13.3)	48 (17.0)	1 (ref.)	-
Former	514 (70.7)	316 (71.0)	198 (70.2)	0.77 (0.51–1.17)	0.22
Current	106 (14.6)	70 (15.7)	36 (12.8)	0.63 (0.36–1.1)	0.12
Obesity (BMI>30)	122 (32.1)	73 (30.7)	49 (34.5)	1.19 (0.77–1.85)	0.44
Hypertension	513 (69.1)	298 (65.0)	215 (75.7)	1.67 (1.2–2.3)	0.002
Hyperlipidemia	396 (53.4)	239 (52.2)	157 (55.3)	1.13 (0.84–1.52)	0.41
Diabetes mellitus	191 (25.8)	119 (26.1)	72 (25.4)	0.96 (0.69–1.35)	0.82
Atrial fibrillation	175 (23.6)	103 (22.5)	72 (25.4)	1.18 (0.83–1.66)	0.36
Myocardial infarction	98 (13.2)	52 (11.3)	46 (16.1)	1.51 (0.98–2.32)	0.059
Heart failure	132 (17.8)	58 (12.7)	74 (26.1)	2.43 (1.65–3.56)	< 0.001
Transient ischemic attack	90 (12.2)	48 (10.5)	42 (15.1)	1.52 (0.97–2.37)	0.066
Dementia	79 (10.6)	36 (7.8)	43 (15.0)	2.08 (1.3–3.33)	0.002
Neurodegenerative disease	71 (9.5)	34 (7.4)	37 (12.9)	1.85 (1.13–3.03)	0.014
Peripheral arterial disease	89 (12.0)	51 (11.1)	38 (13.4)	1.24 (0.79–1.94)	0.35
Chronic kidney disease	82 (11.0)	41 (8.9)	41 (14.4)	1.71 (1.08–2.72)	0.022
Cancer	105 (14.1)	60 (13.1)	45 (15.8)	1.25 (0.82–1.89)	0.30
Obstructive Sleep Apnea Syndrome	130 (17.6)	83 (18.1)	47 (16.9)	0.92 (0.62–1.34)	0.66
Dependency status					
Independent	559 (76.2)	377 (82.7)	182 (65.5)	1 (ref.)	-
Moderate dependency	128 (17.4)	61 (13.4)	67 (24.1)	2.28 (1.54–3.36)	< 0.001
Severe dependency	47 (6.4)	18 (4.0)	29 (10.4)	3.34 (1.81–6.17)	< 0.001
Charlson Comorbidity Index	2 (1–4)	2 (1–4)	3 (2–5)	1.17 (1.09–1.26)	< 0.001
Charlson Comorbidity Index, age corrected	6 (4–8)	5 (4–7)	6 (5–9)	1.23 (1.15–1.32)	< 0.001
Habitual treatment					
Immunosuppressants	27 (3.6)	19 (4.1)	8 (2.8)	0.68 (0.29–1.56)	0.36
Systemic corticosteroids	55 (7.4)	27 (5.9)	28 (9.9)	1.75 (1.01–3.04)	0.046
Inhaled corticosteroids	348 (47.2)	216 (47.2)	132 (47.1)	1 (0.74–1.35)	0.996
Antivitamin K	101 (13.6)	48 (10.5)	53 (18.7)	1.94 (1.27–2.98)	0.002
Antiplatelet Drugs	198 (26.9)	105 (23.0)	93 (33.2)	1.67 (1.20–2.32)	0.002
Statins	374 (50.6)	237 (51.8)	137 (48.8)	0.89 (0.66–1.19)	0.43
ACE In	167 (22.6)	101 (22.1)	66 (23.5)	1.09 (0.76–1.54)	0.65
Angiotensin-renin blockers	185 (25)	107 (23.3)	78 (27.7)	1.26 (0.90–1.77)	0.19

we would also need to have data from non-hospitalized COPD patients.

However, COPD patients with COVID-19 have a poor prognosis. COPD patients are older and have more

comorbidities, especially cardiovascular comorbidities. This association between COPD and comorbidity has previously been described, especially in patients hospitalized for an exacerbation, which is an important prognostic

Table 4 Mortality of COPD Patients with Coronavirus Disease 2019 According to Clinical Data and Treatment

Values are Indicated as the Number (Percentage) or Median (Interquartile Range)					
Characteristics	Overall (n=746)	Survivors (n=460)	Deceased (n=286)	Odds Ratio (95% CI)	P value
Symptoms and vital signs					
Dyspnea	537 (72.3)	304 (66.1)	233 (82.3)	2.39 (1.67–3.43)	<0.001
Temperature >38 °C	95 (13.3)	47 (10.6)	48 (17.5)	1.78 (1.15–2.74)	0.009
Oxygen saturation <90%	283 (38.8)	131 (29.1)	152 (54.3)	0.35 (0.25–0.47)	<0.001
Oxygen saturation % Median (IQR)	92 (88–95)	93 (90–96)	90 (86–94)	0.91 (0.88–0.93)	<0.001
Respiratory rate >20 breaths/min	348 (47.9)	169 (37.6)	179 (64.6)	3.03 (2.22–4.13)	<0.001
Heart rate					
>100 beats/min	145 (20.0)	80 (17.9)	65 (23.4)	1.40 (0.97–2.02)	0.073
Median (IQR)	85 (75–98)	85 (74–98)	86 (76–100)	1.01 (0.99–1.01)	0.18
SBP, median (IQR) mmHg	127 (113–144)	129 (116–144)	125 (110–141)	0.99 (0.99–1)	0.09
DBP, median (IQR) mmHg	72 (61–80)	73 (64–81)	70 (60–80)	0.99 (0.98–0.99)	0.008
Confusion	127 (17.3)	53 (11.7)	74 (26.3)	2.71 (1.83–4)	<0.001
Radiological findings					
At admission					
Bilateral condensation	203 (27.7)	107 (23.7)	96 (33.9)	1.8 (1.29–2.6)	0.001
Bilateral interstitial infiltrates	359 (48.9)	202 (44.7)	157 (55.7)	1.6 (1.13–2.15)	0.006
Progress (7 days)					
Bilateral condensation	198 (36.5)	114 (30.7)	84 (49.1)	2.38 (1.58–3.57)	< 0.001
Bilateral interstitial infiltrates	316 (58.1)	201 (53.9)	115 (67.3)	1.55 (1.03–2.32)	0.035
Radiological worsening	277 (50.8)	147 (39.6)	130 (74.7)	4.5 (3.02–6.72)	< 0.001
Treatment					
Lopinavir/ritonavir	421 (56.9)	267 (58.4)	154 (54.4)	0.85 (0.63–1.45)	0.29
Interferon-beta	94 (12.8)	41 (9.0)	53 (19.0)	2.36 (1.52–3.66)	< 0.001
Remdesivir	4 (0.6)	2 (0.4)	2 (0.7)	1.66 (0.23–11.85)	0.61
Hydroxychloroquine	610 (82.4)	398 (87.1)	212 (74.9)	0.44 (0.3–0.65)	< 0.001
Chloroquine	26 (3.5)	16 (3.5)	10 (3.6)	1.02 (0.46–2.29)	0.96
Colchicine	10 (1.4)	4 (0.9)	6 (2.2)	2.5 (0.7–8.9)	0.16
Tocilizumab	50 (6.8)	23 (5.0)	27 (9.6)	1.99 (1.12–3.56)	0.019
Immunoglobulin	2 (0.3)	1 (0.2)	1 (0.4)	1.7 (0.1–26.6)	0.72
Anakinra	4 (0.6)	3 (0.7)	1 (0.4)	0.54 (0.06–5.24)	0.60
Systemic corticosteroids	364 (49.3)	215 (47.1)	149 (53.0)	1.27 (0.94–1.71)	0.12
Beta-lactams	561 (76.3)	329 (72.3)	232 (82.9)	1.85 (1.28–2.69)	0.001
Macrolides	400 (55.0)	263 (57.9)	137 (50.0)	0.73 (0.54–0.98)	0.037
Quinolones	134 (18.5)	78 (17.2)	56 (20.5)	1.24 (0.85–1.82)	0.27
Non-invasive mechanical ventilation	74 (10.1)	34 (7.5)	40 (14.4)	2.09 (1.29–3.40)	0.003
High-flow nasal cannula	96 (13.2)	46 (10.2)	50 (18.0)	1.93 (1.25–2.97)	0.003
Invasive mechanical ventilation	36 (4.9)	8 (1.8)	28 (10.1)	6.27 (2.82–13.97)	<0.001
Prone position	82 (11.2)	25 (5.5)	57 (20.6)	4.44 (2.70–7.29)	<0.001
Hospital stay in days, median (IQR)	10 (6–16)	12 (7–17)	7 (3–12)	0.95 (0.93–0.96)	<0.001

factor. Almagro confirmed the elevated prevalence of associated diseases in patients with COPD who are admitted to the Spanish Internal Medicine Services; in a later article he showed that mortality at 3 months in hospitalized COPD patients was associated with comorbidities both measured with the Charlson index and total of comorbidities.^{2,16}

Roberts demonstrated that comorbidities adversely affect in hospitalized COPD exacerbations.¹⁷ Alqahtani in a systematic review and meta-analysis found that heart failure, renal failure, depression and alcohol use were all associated with an increased risk of 30-day all-cause readmission.¹⁸ The association between comorbidities

Table 5 Comorbidity and mortality of COPD Patients with Coronavirus Disease 2019

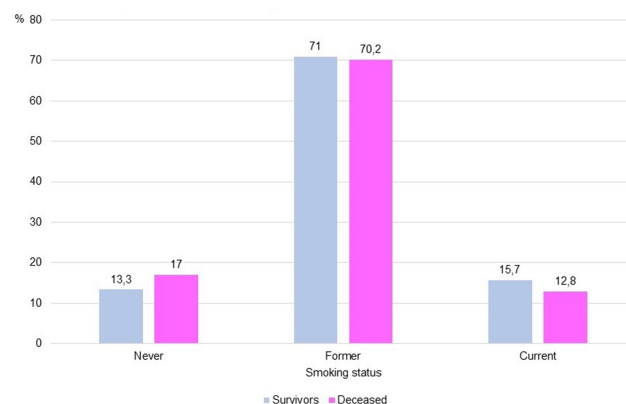
Characteristics	Overall (n=746)	Survivors (n=460)	Deceased (n=286)	Odds Ratio (95% CI)	P value
Comorbidity - CVRF^a					
No	169 (22.6)	111 (24.1)	58 (20.3)	1 (ref.)	–
Yes	577 (77.4)	349 (75.9)	228 (79.7)	1.25 (0.87–1.79)	0.22
Comorbidity - NRL^b					
No	583 (78.2)	373 (81.1)	210 (73.4)	1 (ref.)	–
Yes	163 (21.9)	87 (18.9)	76 (26.6)	1.55 (1.09–2.20)	0.014
Comorbidity - Cardio^c					
No	406 (54.4)	266 (57.8)	140 (49.0)	1 (ref.)	–
Yes	340 (45.6)	194 (42.2)	146 (52.0)	1.43 (1.06–1.92)	0.018
Comorbidity - K.L^d					
No	614 (82.3)	387 (84.1)	227 (79.4)	1 (ref.)	–
Yes	132 (17.7)	73 (15.9)	59 (20.6)	1.38 (0.94–2.02)	0.10
Comorbidity - Onco^e					
No	623 (83.5)	392 (85.2)	231 (80.8)	1 (ref.)	–
Yes	123 (16.5)	68 (14.8)	55 (19.2)	1.37 (0.93–2.03)	0.11
Comorbidity^f					
No	64 (8.6)	51 (11.1)	13 (4.5)	1 (ref.)	–
Yes	682 (91.4)	409 (88.9)	273 (95.5)	2.62 (1.40–4.91)	0.003

Notes: ^aComorbidity-CVRF: Considering as comorbidity the presence of any of the following Cardiovascular Risk Factors: HBP, Dyslipidemia, Diabetes Mellitus (with or without target organ injury) or Obesity. ^bComorbidity-NRL: We consider as comorbidity the presence of any of the following pathologies: Dementia, Neurodegenerative disease, Transient ischemic attack, Acute cerebrovascular accident, Hemiplegia. ^cComorbidity-Cardio: We consider as comorbidity the presence of any of the following pathologies: Atrial fibrillation, myocardial infarction, Angor, CHF, Peripheral vascular disease. ^dComorbidity-K.L: We consider as comorbidity the presence of any of the following pathologies: chronic kidney disease or Hemodialysis, mild or moderate–severe chronic liver disease. ^eComorbidity-Onco: We consider as comorbidity the presence of any of the following pathologies: solid neoplasia with or without metastasis, leukemia or lymphoma. ^fComorbidity: In this case we consider as comorbidity the presence of any of the pathologies included in the previous ones.

and the severity of SARS-CoV-2 infection has also been described, finding that greater severity is correlated with increased comorbidity. Thus, the presence of two or more comorbidities was observed more frequently in severe cases than in non-severe cases (40.0% vs 29.4%).⁴ In our work, the Charlson Comorbidity Index, a comorbidity index that has been validated as a prognostic factor in

COPD, is also associated with a worse prognosis in patients with COVID-19. Although obesity is considered a risk factor in COVID, in our work it is not related to mortality in COPD patients.¹⁹ This may be justified by a protective effect of obesity on all-cause mortality in COPD patients, described in several studies. This protection is more evident for subjects with a lower FEV1.²⁰ Several mechanisms have been proposed that may explain why COVID-19 is more frequent in male patients, elderly with multimorbidity. The higher incidence in men may be associated with the fact that androgen receptor activity is required for the transcription of the TMPRSS2 gene.

In old age there is multisystem dysregulation with a reduced physiological reserve and a poor immune response. In an aging immune system there is a chronic low systemic inflammatory state with elevated levels of IL-6 and C-reactive protein and increased susceptibility to infection. In diabetes there is a low-grade systemic inflammation, which can facilitate a greater release of cytokines and an altered immune response after infection. The pancreas expresses ECA2, through which the coronavirus can

**Figure 1** Mortality according to smoking status in COPD with COVID-19.

enter the islets and cause acute B-cell dysfunction, leading to acute hyperglycemia. Many of the poor prognostic comorbidities of COVID-19 share insulin resistance. Multimorbidity is also associated with elevated plasminogen levels. Plasmin and other proteases can cleave a newly inserted furin site in the SARS-CoV-2 protein S, increasing its infectivity and virulence.²¹

Some coronaviruses have been associated with exacerbations of COPD, but neither MERS-CoV nor SARS-CoV-1 showed this association.^{22,23} The presentation of COVID-19 in patients with COPD has been described as different from an exacerbation of COPD, since they present with flu-like symptoms such as fever, anorexia, myalgia, and gastrointestinal symptoms.²⁴ However, in the patients analyzed in this study, the usual presentation included increased dyspnea and expectoration and the presence of rhonchi and wheezing on auscultation, similar to a normal infectious exacerbation. Based on this, we recommend performing a SARS-CoV-2 test in all COPD patients with symptoms of exacerbation.

In our series, as in others, COPD patients hospitalized for COVID-19 have a high mortality rate and COPD is considered a predictor of poor prognosis. In the work by Wang et al, patients with COPD were found to be 5.9 times more at risk of suffering severe forms of COVID-19 than patients without COPD.²⁵ In the work by Zhao et al, the presence of COPD entailed a four-fold risk of suffering a serious course of COVID-19.⁹ Alqahtani et al indicate that the presence of COPD increased the risk of severe coronavirus, with a RR of 1.88. They found that 63% of patients with COPD developed severe forms of the disease compared to 33.4% of those without COPD, with a mortality rate of 60% among patients with COPD.¹⁰ In patients older than age 60 who are diagnosed with COVID-19, COPD was a predictor of death, (OR 2.24).²⁶ In a meta-analysis, COPD was associated with an increased mortality risk, (OR 3.53).²⁷ In the work by Lippi, COPD was significantly associated with severe COVID-19, OR: 5.69.²⁸ COPD has also been described as a risk factor for disease progression (HR 2.01, 95% CI 1.38–2.93).²⁹ It is possible that poor prognosis depends only on the COPD itself or it may be partially associated with the multimorbidity of these patients.

Smokers are at higher risk of contracting respiratory tract infections such as influenza, and that these are more serious, as in the previous MERS outbreak where smokers had a higher mortality. A low prevalence of smoking has been found in COVID-19 cases, although published data

on the severity of COVID-19 in smokers is variable. In a meta-analysis, active smokers were found to be 1.45 times more likely to have serious complications compared to ex-smokers and those who had never smoked. They also had a higher mortality rate of 38.5%. In another work, the combined OR was 2.20. However, in other studies, the association between active smoking and severe COVID-19 was not found to be significant. It has even been reported that smoking may be associated with a non-significant trend towards decreased severity of the disease and perhaps even a protective factor against disease progression (HR 0.56, 95% CI 0.34 at 0.91). Vardavas in a systematic review of studies concludes that it is very likely that smoking is associated with poor progression and poor prognosis of COVID-19.

It has been postulated that the infection is more severe in patients with COPD and in smokers because exposure to tobacco causes an alteration in the regulation of ACE-2 expression, these patients presenting an overexpression of ACE-II, the receptor of the virus to enter the cell; furthermore, the expression levels of ACE-II are inversely related to FEV1. However, in our study, the smoking status has not been related to all-cause mortality. It is also proposed that in smokers the immune system is impaired, with an altered response of macrophages and cytokines, and the inflammatory cascade that occurs in SARS-CoV-2 infection could be especially catastrophic. Another hypothesis is that nicotine may have a protective effect on COVID-19, which disappears due to the abrupt cessation of nicotine intake when smokers are hospitalized.^{5,9,10,29–34}

Classically, mortality in COPD has been associated with FEV1. It is now known that its predictive value is low when it is greater than 50% of what was expected and that there are other clinical variables that predict mortality better than FEV1, as reflected in the different multicomponent prognostic indices in COPD. In our work, no association was found between FEV1 and all-cause mortality.^{35,36}

Scientific societies advise maintaining the usual treatment and management of exacerbation in COPD patients according to current recommendations. The best way to prevent and reduce the severity of exacerbations in respiratory infections in patients with COPD is optimal drug treatment. There is no evidence that inhaled corticosteroids increase the risk of or worsen SARS-CoV-2 infection. In an exacerbation of COPD with concurrent SARS-CoV-2 infection, it is advisable to follow the indications for treatment with corticosteroids recommended in the guidelines, although efforts should be made to limit the dose and

duration of the corticosteroids due to the possibility of increasing viral replication.^{37,38}

In our work, COPD patients who were in regular treatment with systemic corticosteroids had a higher mortality rate. This could possibly be a reflection of more severe COPD with worse functional capacity in addition to possible immunosuppression associated with the use of systemic corticosteroids, which would entail a higher viral load and greater SARS-CoV-2 involvement.

A better prognosis was not found in patients treated with lopinavir/ritonavir or systemic corticosteroids. The study by Cao et al also found no benefits in the use of lopinavir/ritonavir in hospitalized patients with severe COVID-19 pneumonia, although the study was probably underpowered.³⁹

We found a higher survival rate in patients treated with hydroxychloroquine and with macrolides. Azithromycin is frequently used for exacerbations of COPD, but it has emerged as a possible complementary therapy with hydroxychloroquine for COVID-19. Azithromycin has immunomodulatory activity and, presumably, antiviral activity. Hydroxychloroquine would have activity at various levels: on the one hand, it acts through ACE2, attenuating the entry of SARS-CoV-2 into the pulmonary epithelium and, on the other hand, it can have immunosuppressive effects by reducing IL-6 production in T cells and monocytes. Caution is advised in trials evaluating azithromycin along with hydroxychloroquine for its effects on QT segment prolongation and propensity for arrhythmias.^{40–42} Regarding hydroxychloroquine, our study is not designed to verify its usefulness in treatment and at present, its use is only recommended in clinical trials. Further studies are required to determine the usefulness of azithromycin and/or hydroxychloroquine treatment in COPD patients with SARS-CoV-2 infection.

SARS-CoV2 infection produces immunosuppression with lymphopenia, suppression of interferon, and defective NK cell function. This loss of the antiviral defense mechanism can activate a more aggressive “second wave” of immunity, with a cytokine storm, with very high levels of ferritin, C-reactive protein and IL-1 β , IL-2, IL-6, IL-17, IL-8 and TNF. We also found an elevated D-dimer as a representation of the extension of this hyper-inflammatory state to the adjacent microcirculation with secondary fibrinolytic activation that would be associated with extensive pulmonary microthrombosis. This immune hyperactivity is more confined to the lung parenchyma and adjacent bronchial alveolar lymphoid tissue and is associated with the development of an acute respiratory

distress syndrome that may require ventilatory support. This condition is similar to the macrophage activation syndrome seen in some systemic diseases, but located in the lung, which is not usually accompanied by organomegaly or disseminated intravascular coagulation. Anti-IL-6 and anti-IL-1 medications are being used to prevent this. In our study, however, so few patients were treated with tocilizumab or anakinra that no conclusions or recommendations can be drawn.^{43–47}

With the data we have so far and given the severity of COVID-19, it may be necessary to consider combination treatment for COPD patients with action at two levels: one to avoid the binding of SARS-CoV-2 to lung tissue and another that blocks the cytokine storm that is released.⁴⁷

This work has several limitations. First, the data included in the registry are collected by a large team of researchers. Second, many patients have a history of COPD, but spirometric data are not always included and as such, the registry could include patients who have not been properly diagnosed of COPD. Third, 26% of non-COPD patients reported being smokers or ex-smokers. Taking into account the underdiagnosis of COPD in the population, it is logical to assume that the prevalence of patients with COPD is higher. Lastly, in the SEMI-COVID registry, data on chronic treatment with inhalers were not included, so we have not been able to analyze if LAMA and/or LABA could have a protective effect on SARS-CoV-2 lung infection.¹⁵

Conclusion

Although patients with COPD do not seem to have a higher risk of contracting SARS-CoV-2 infection, they do have a worse prognosis, especially in patients with greater comorbidity. These patients must be identified early in order to establish preventive measures that reduce risk and provide adequate management.

Acknowledgments

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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