



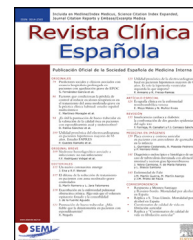
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ORIGINAL ARTICLE

Patients with COPD hospitalized due to COVID-19 in Spain: a comparison between the first and second wave

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KEYWORDS

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Abstract

Objective: This work aimed to compare the characteristics, progress, and prognosis of patients with COPD hospitalized due to COVID-19 in Spain in the first wave with those of the second wave.

Material and methods: This is an observational study of patients hospitalized in Spain with a diagnosis of COPD included in the SEMI-COVID-19 registry. The medical history, symptoms, analytical and radiological results, treatment, and progress of patients with COPD hospitalized in the first wave (from March to June 2020) versus those hospitalized in the second wave (from July to December 2020) were compared. Factors associated with poor prognosis, defined as all-cause mortality and a composite endpoint that included mortality, high-flow oxygen therapy, mechanical ventilation, and ICU admission, were analyzed.

Results: Of the 21,642 patients in the SEMI-COVID-19 Registry, 6.9% were diagnosed with COPD: 1128 (6.8%) in WAVE1 and 374 (7.7%) in WAVE2 ($p = 0.04$). WAVE2 patients presented less dry cough, fever and dyspnea, hypoxemia (43% vs 36%, $p < 0.05$), and radiological condensation (46% vs 31%, $p < 0.05$) than WAVE1 patients. Mortality was lower in WAVE2 (35% vs 28.6%, $p = 0.01$). In the total sample, mortality and the composite outcome of poor prognosis were lower among patients who received inhalation therapy.

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¹ A full list of the SEMI-COVID-19 Network members can be found in Appendix A.

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PALABRAS CLAVE

COPD;
COVID-19;
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Primera y segunda ola
de infección;
Prognosis

Conclusions: Patients with COPD admitted to the hospital due to COVID-19 in the second wave had less respiratory failure and less radiological involvement as well as a better prognosis. These patients should receive bronchodilator treatment if there is no contraindication for it.
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Pacientes con EPOC hospitalizados por COVID-19 en España: comparación entre la primera y la segunda ola

Resumen

Objetivo: Comparar las características, evolución y pronóstico de los pacientes con EPOC hospitalizados por COVID-19 en España en la primera ola con los de la segunda ola.

Material y métodos: Estudio observacional de los pacientes hospitalizados en territorio español con diagnóstico de EPOC incluidos en el registro SEMI-COVID-19.

Se compararon los antecedentes, la clínica, resultados analíticos y radiológicos, tratamiento y evolución de los pacientes con EPOC hospitalizados en la primera ola (desde marzo hasta junio 2020) frente a los hospitalizados en la segunda ola (desde julio hasta diciembre 2020). Se analizaron los factores de mal pronóstico, definidos como mortalidad por todas las causas y un evento combinado que incluía mortalidad, oxigenoterapia con alto flujo, ventilación mecánica e ingreso en UCI.

Resultados: De 21,642 pacientes del Registro SEMI COVID-19, están diagnosticados de EPOC el 6,9%, 1128 (6,8%) en la OLA1 y 374 (7,7%) en la OLA2 ($p = 0,04$). Los pacientes de la OLA2 presentan menos tos seca, fiebre y disnea, hipoxemia (43% vs 36%, $p < 0,05$) y condensación radiológica (46% vs 31%, $p < 0,05$) que los de la OLA1. La mortalidad es menor en la OLA2 (35% vs 28,6%, $p = 0,01$). En el global de pacientes la mortalidad y la variable combinada de mal pronóstico fue menor entre los pacientes que recibieron tratamiento inhalador.

Conclusiones: Los pacientes con EPOC con ingreso hospitalario por COVID-19 en la segunda ola presentan menos insuficiencia respiratoria y menos afectación radiológica, con mejor pronóstico. Estos pacientes deben recibir tratamiento broncodilatador si no hay contraindicación para el mismo.

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Introduction

SARS-CoV-2 infection started in China at the end of 2019 and then spread to the rest of the world, with a progressive increase in the number of cases reported. The peak of infections in Europe occurred in April 2020, with a decline until June. This is referred to as the first wave because in July 2020, another progressive increase in cases started, giving rise to the second wave.¹

It was expected that a significant part of patients hospitalized due to COVID-19 in the first wave would have been patients with COPD. However, it was observed that there were fewer than expected, as different registries have shown. A total of 7.7% of patients in the SEMI-COVID-19 registry² had COPD compared to 5.4% in a series from the New York area.³

In the works published on the first wave, patients with COPD hospitalized due to COVID-19 had more severe disease, a worse prognosis, and a mortality rate of up to 40%.⁴⁻⁶

After the experience and large amount of scientific research generated after the first wave, it is to be expected

that the management and prognosis of patients with COPD and COVID-19 would improve in the second wave.

This work aims to compare the characteristics, progress, and prognosis of patients with COPD hospitalized due to COVID-19 in the first and second waves.

Materials and methods

Observational study

Data were collected from patients included in the SEMI-COVID-19 registry, a retrospective cohort which included consecutive patients hospitalized in Spain from March 2020 with confirmed SARS-CoV-2 infection who were discharged after hospitalization or who died. The registry inclusion criteria were: a) patient age ≥ 18 years; b) confirmed COVID-19 diagnosis; c) index hospitalization in a Spanish hospital participating in the registry; d) hospital discharge or in-hospital death. COVID-19 disease was confirmed through a positive result on a real-time polymerase chain reaction (RT-PCR)

test of a nasopharyngeal or sputum sample or a positive result on serological tests and a clinically compatible presentation. The description, characteristics, and baseline results of the SEMI-COVID-19 registry can be consulted in the work published by Casas-Rojo et al.²

Patients diagnosed with COPD were selected from the SEMI-COVID-19 registry without needing to have a confirmatory spirometry. Patients hospitalized from March to June 2020 were considered to belong to the first wave (WAVE1) and those hospitalized from July to December 2020 were considered to belong to the second wave (WAVE2).

The variables selected for the analysis were demographic variables; medical history; comorbidities; chronic treatment; signs and symptoms of patients upon admission; analytical data; radiological findings; treatment received upon admission; radiological progress; ventilatory support: high-flow nasal cannula (HFNC) oxygen therapy, noninvasive mechanical ventilation (NIMV), or invasive mechanical ventilation (IMV); admission to the ICU; and death.

The medical history, symptoms, analytical and radiological results, treatment, and clinical progress of patients with COPD hospitalized in the first wave were compared to those hospitalized in the second wave. Factors associated with poor prognosis, defined as all-cause mortality and a composite variable that included mortality; need for HFNC oxygen therapy, NIMV, or IMV; or ICU admission were analyzed.

The calculations for the descriptive analysis were performed using the EXCEL computer program using the dynamic tables tool and the advanced data analysis feature. Qualitative variables were expressed as absolute frequency (n) and percentage (%). Quantitative variables were expressed as medians, interquartile range, and range with a 95% confidence interval. The Student's *t*-test was used. Statistical significance was defined as $p < 0.05$. A logistic regression analysis was performed using the R statistical program to control for confounding bias. To do so, WAVE1 was treated as the cause or independent variable, mortality and the composite variable as the dependent variable, and respiratory failure and radiological involvement as possible confounding factors because they were found to be associated with mortality. The regression coefficients obtained on two different models were compared and when the magnitude of the change in OR was close to or greater than 10%, it was considered that there was confounding bias.

Ethical considerations

Personal data were 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 27 April 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing 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 approved for the first time by the Provincial Research Ethics Committee of Málaga (Spain), following the recommendation of the Spanish Agency of Medicines and Health Products (AEMPS, for its initials in Spanish). Informed consent was requested from all patients. When it was not

possible to obtain it in writing due to biosafety issues or because the patient was already discharged from the hospital, verbal informed consent was requested and recorded on the medical record.

Results

Of a total of 21,642 patients in the SEMI-COVID-19 Registry, 1502 patients (6.9%) had been diagnosed with COPD. Of them, 1128 (6.8%) corresponded to WAVE1 and 374 (7.7%) to WAVE2. The proportion of patients with COPD hospitalized due to COVID-19 was significantly greater in WAVE2 ($p < 0.05$).

Eighty-two percent of patients in the first wave and 88% of patients in the second wave were men. Thirty-six percent of patients in WAVE1 and 46% of patients in WAVE2 were older than 80 years (Table 1).

The clinical presentation of patients with COPD continued to mainly be dyspnea, fever, and dry cough, but in the second wave, patients presented with significantly less dry cough, fever, and dyspnea ($p < 0.05$). Differences were found in hypoxemia, with 43% of patients in WAVE1 and 36% of patients in WAVE2 presenting with $\text{SatO}_2 < 92\%$ ($p < 0.05$). Patients in WAVE2 presented with more kidney failure (42% vs 50%, $p < 0.05$) and less radiological condensation (46% vs 31%, $p < 0.05$) than those in WAVE1 (Table 1). Symptoms differed somewhat in women, who presented with more nonspecific symptoms such as arthromyalgia (27% vs 21%, $p < 0.05$), headache (13% vs 5%, $p < 0.05$), and absence of fever or low-grade fever (59% vs 47%, $p < 0.05$).

There were differences in the treatments used in both waves. In WAVE2, lopinavir/ritonavir, hydroxychloroquine, and chloroquine were not used; 15% of patients received remdesivir (1% in WAVE1); and 88% of patients received treatment with systemic glucocorticoids, compared to 51% in the first wave. Fewer antibiotics were used (82% vs 91%) and a lower rate of polypharmacy was observed in patients in WAVE2.

The overall mortality rate in patients with COPD was 33.4%: 35% in WAVE1 and 28.6% in WAVE2. Mortality declined in the second wave, with the decline being greater than what occurred in the total population of patients with COVID-19 (Fig. 1). Mortality was greater in men with COPD than in women (35.2% vs 24.5%, $p < 0.001$) and declined in WAVE2, with the decline being greater in women: 26.1% vs 17.4%.

The probability of death in those older than 80 years is significantly greater than in the rest of patients ($p < 0.05$). Nearly all comorbidities increased mortality, but only HT (WAVE1: 38.4% vs WAVE2: 29.3%, $p = 0.005$) and obesity (40.4% vs 27.9%, $p = 0.018$) significantly increased mortality between waves.

In all patients with COPD, the presence of dyspnea is an indicator of poor prognosis (49% vs 30%, $p < 0.05$) and mortality (37.3% vs 23.2%, $p < 0.05$). On the contrary, patients who had anosmia (mortality 11.5% vs 34.2%, $p < 0.05$), ageusia (mortality 14.8% vs 34%, $p < 0.05$), or arthromyalgias (mortality 27% vs 35.2%, $p < 0.05$) had a better prognosis.

Patients with $\text{SatO}_2 < 92\%$, creatinine > 1.2 mg/dL, or bilateral lung lesions on radiologic tests had greater mortality and a worse prognosis (Table 2). No differences were found between waves in levels of procalcitonin or D-dimer.

Table 1 Characteristics of patients with COPD hospitalized due to COVID-19. Comparison between WAVE1 and WAVE2.

	Total (1502)	WAVE1 (1128)	WAVE2 (374)	<i>p</i> WAVE1 vs WAVE2
Men	84%	82%	88%	<i>p</i> < 0.01
>80 years	39%	36%	46%	
HT	70%	69%	72%	NS
Dyslipidemia	54%	54%	54%	NS
AF	23%	24%	22%	NS
Obesity	28%	28%	30%	NS
Dry cough	45%	48%	36%	<i>p</i> < 0.05
Fever	50%	52%	44%	<i>p</i> < 0.05
Dyspnea	72%	74%	66%	<i>p</i> < 0.05
SatO ₂ < 92%	41%	43%	36%	<i>p</i> < 0.05
Kidney failure	44%	42%	50%	<i>p</i> < 0.05
Radiological condensation	43%	46%	31%	<i>p</i> < 0.05
Prone positioning	11%	12%	6%	NS
HFNC oxygen therapy	13%	12%	14%	NS
NIMV	11%	11%	10%	NS
IMV	6%	6%	7%	NS
ICU	8%	8%	10%	NS
Mortality	33.4%	35%	28.6%	<i>p</i> < 0.05

HT: hypertension. AF: atrial fibrillation. SatO₂: pulse oxymetry oxygen saturation. Renal failure: creatinine >1.2 mg/dL. HFNC: high-flow nasal cannula oxygen therapy. NIMV: non-invasive mechanical ventilation. IMV: invasive mechanical ventilation. ICU: intensive care unit.

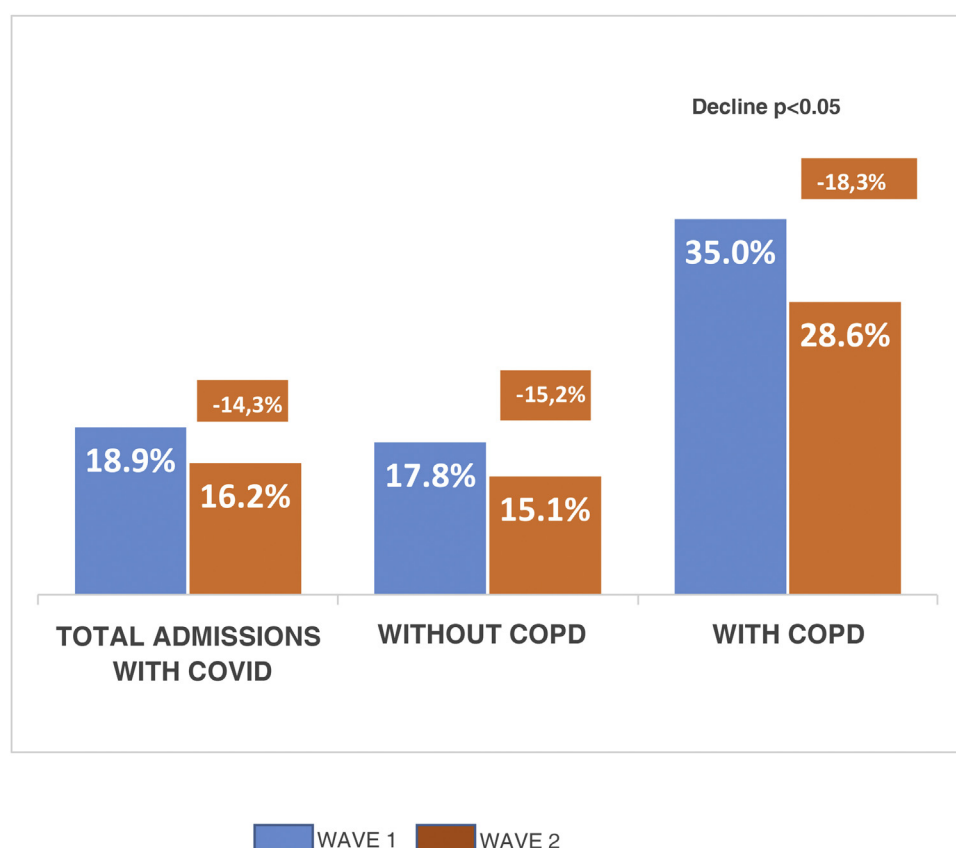


Figure 1 Mortality in total admissions due to COVID-19, mortality in patients with and without COPD and decline in mortality in WAVE1 and WAVE2.

No differences in mortality were found among patients with chronic habitual use of inhaled corticosteroids, inhaled beta-adrenergics, and inhaled anticholinergics compared to

patients who did not use them. Patients treated with systemic glucocorticoids had greater overall mortality (47.1% vs 32.2%, *p* < 0.001) and a worse prognosis on the combined

Table 2 Indicators of a poor prognosis in patients with COPD hospitalized due to COVID-19.

	Total mortality	Mortality WAVE1	Mortality WAVE2	<i>p</i> WAVE1 vs WAVE2	Poor overall prognosis	Poor prognosis WAVE1	Poor prognosis WAVE2	<i>p</i> WAVE1 vs WAVE2
	33%	35%	28.6%		44%	46%	38%	
Confusion	52%	54%	47%	<i>p</i> <0.05	62%	64%	57%	<i>p</i> < 0.05
Tachypnea	46%	47%	40%	<i>p</i> <0.05	59%	60%	53%	<i>p</i> < 0.05
SatO ₂ * <92%	45%	46%	43%	<i>p</i> <0.05	59%	60%	55%	<i>p</i> < 0.05
Creatinine >1.2 mg/dL	44%	46%	39%	<i>p</i> <0.05	53%	56%	47%	<i>p</i> < 0.05
Bilateral condensation on X-ray**	44%	46%	36%	<i>p</i> <0.05	54%	57%	42%	<i>p</i> < 0.05
Bilateral interstitial pattern on X-ray**	39%	40%	34%	<i>p</i> < 0.05	52%	54%	48%	<i>p</i> < 0.05

* SatO₂: pulse oxymetry oxygen saturation.

** X-ray: chest X-ray.

variable (57% vs 43%, *p* < 0.001) than those who did not use them.

Among all patients, those who received inhaled therapy had lower mortality (35.8% vs 27.3%, *p* < 0.05) and a lower percentage on the composite poor prognosis variable (46% vs 39%, *p* < 0.05). Patients who received beta-adrenergics had lower mortality (23% vs 33%, *p* < 0.05). Those who received ipratropium (30% vs 44%, *p* < 0.05; 35% vs 44%, *p* < 0.05, respectively) had a better prognosis on the combined variable (Fig. 2).

Patients who did not receive any antibiotics had a lower mortality rate (25% vs 33%, *p* < 0.05) and a better prognosis (35% vs 44%, *p* < 0.05) than the mean. Comparing other treatments received during hospitalization (angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), statins, acetylsalicylic acid (ASA), low-molecular-weight heparin (LMWH)), there were no differences in mortality or the composite poor prognosis variable except for LMWH at full anticoagulation doses, which was associated with a poor prognosis (55% vs 44%, *p* < 0.05).

On the regression analysis, WAVE1 was treated as the main independent variable and mortality and the composite poor prognosis variable as the dependent variable. Respiratory failure and radiological involvement were treated as possible confounding factors. If respiratory failure and radiological involvement are analyzed separately, there is no sufficiently strong statistical evidence that these factors are responsible for the differences in mortality and poor prognosis between waves. On the contrary, when the two factors are analyzed jointly, there are differences (Table 3).

Discussion

According to other published works, the percentage of patients with COPD hospitalized due to COVID-19 is lower than the overall prevalence of the disease in the population. In the previously reported SEMI-COVID-19 registry, the prevalence of COPD in the first wave was 7.6% and the prevalence in this study is 6.9%, a variation that may be due to the inclusion of more cases following publication of the initial

study. However, in this series, the proportion of patients with COPD increased significantly in the second wave compared to the first.²⁻⁴

Previous works have described that patients with COPD who are hospitalized due to SARS-CoV-2 infection are predominantly men; are older adults; have high comorbidity; have symptoms which consist of an increase in dyspnea and expectoration with fever or low-grade fever; and present with hypoxemia, tachypnea, and confusional syndrome upon admission.⁴

This work found that patients in the second wave continued to mainly be older men. These patients in the second wave presented with fewer symptoms, less respiratory failure, and less condensation on radiological tests. This suggests that patients in WAVE2 arrived to the hospital earlier, with less advanced disease, and in better condition than in WAVE1. This could have been influenced by the general population's better knowledge on the disease and its symptoms and consequently, patients may have consulted sooner; an improvement in diagnostics, with an earlier diagnosis and a diagnosis in milder phases; less collapse of the healthcare system; and a change in virologic pattern given that in the second wave, the mean viral load value was lower and the highest levels were detected among younger patients, which could be explained by a lower level of viral inoculation as a consequence of the use of masks, social distancing, and restrictions on gatherings.¹⁻⁹

As previous publications have described, age continues to be one of the main prognostic factors in SARS-CoV-2 infection in patients with COPD.

Although mortality decreased in the second wave, the mortality rate in patients with COPD is nearly double that of the population without COPD. In addition to this, the older age of patients with COPD than the rest of the hospitalized population and the high comorbidity of patients with COPD, especially cardiovascular disease, diabetes, and obesity, are clear factors of a poor prognosis in COVID-19. In this work, the comorbidity of patients with COPD continues to be very high, with no differences between the two waves, as has been reported in other publications.^{4,10,11}

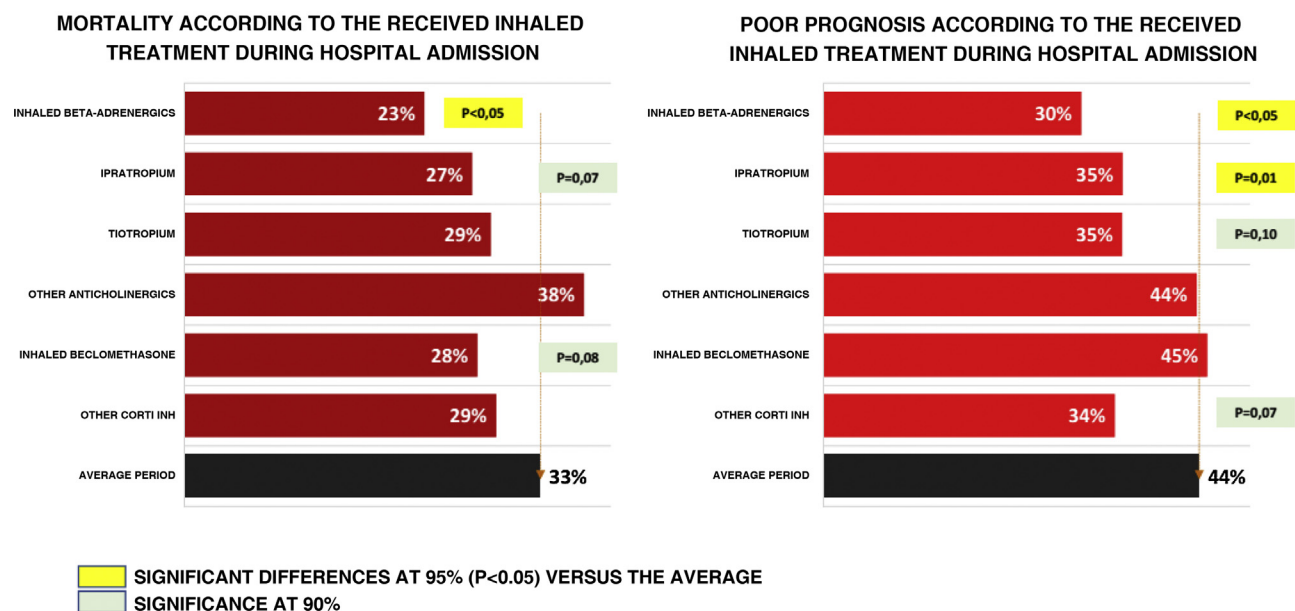


Figure 2 Patients with COPD admitted to the hospital due to COVID-19 in the first and second wave. Mortality and poor prognosis according to the received inhaled treatment during hospital admission.

Table 3 Characteristics of patients with COPD hospitalized due to COVID-19. Logistic regression study.

Results for mortality

	Crude OR (95% CI)	Adjusted OR (95% CI)	Magnitude difference
SatO ₂ * <92%	1.34 (1.04–1.74)	1.28 (0.99–1.86)	4.80%
Bilateral condensation on X-ray**	1.34 (1.04–1.74)	1.26 (0.98–1.64)	6.10%
SatO ₂ * <92% + Bilateral condensation on X-ray**	1.34 (1.04–1.74)	1.21 (0.93–1.58)	9.80%

Results for the composite poor prognosis variable

	Crude OR (95% CI)	Adjusted OR (95% CI)	Magnitude difference
SatO ₂ * <92%	1.39 (1.1–1.78)	1.33 (1.04–1.7)	4.80%
Bilateral condensation on X-ray**	1.39 (1.1–1.78)	1.33 (1.04–1.69)	5.10%
SatO ₂ * <92% + Bilateral condensation on X-ray**	1.39 (1.1–1.78)	1.28 (0.99–1.64)	8.70%

OR: odds ratio.

* SatO₂: pulse oxymetry oxygen saturation.

** X-ray: chest X-ray.

The better prognosis in women is notable, with a greater decline in mortality in the second wave than in men with COPD. One of the hypotheses that could explain this difference due to sex is based on the role of sex in the genetic and hormonal regulation of immune responses and in the different ACE2 activity between men and women; men with hypertension and heart failure tend to have a higher level of ACE2 serum activity compared to women.^{12,13}

There was a lower mortality and better prognosis in WAVE2. In a work comparing mortality in the two waves in Japan, mortality was also lower in the second wave, even when stratified by age and severity upon admission. The authors linked this to a shorter period of time between disease onset and admission and that the patients had milder disease upon admission.¹⁴ After the regression analysis in this series, it was also observed that the patients' better clinical situation—reflected in the com-

bination of lesser respiratory failure and lesser radiologic involvement—would be behind the lower mortality rate and better prognosis observed in WAVE2. Other works have suggested that the pattern of inflammation in the second wave—measured through biomarkers such as LDH, ferritin, CRP, IL-6, and D-dimer—was lower. This was not able to be confirmed in this series, in which no differences were found in the lymphocytes or D-dimer figures between the waves.¹⁵

Contou et al. described less of a need for invasive mechanical ventilation in the second wave of patients hospitalized in the ICU, but did not find any differences in mortality. Other authors have also reported greater use of non-invasive mechanical ventilation in the second wave. In this study, no differences were found between waves in the need for high-flow oxygen therapy, non-invasive or invasive mechanical ventilation, or ICU admission.¹⁶

One of the factors that contributed to the improvement in patients' prognosis in the second wave is undoubtedly the fact that Spain's healthcare system was better prepared than in the first wave; more diagnostic tests were performed and performed earlier; and there was more experience with and scientific evidence on treatment. In the second wave, drugs such as lopinavir/ritonavir or hydroxychloroquine were no longer used whereas remdesivir, tocilizumab were used; most patients (88% in this series) received systemic glucocorticoids. There was less polypharmacy in the second wave and lesser use of antibiotics, which was also described by Brehm, who additionally reported fewer nosocomial infections.¹⁷

In this work, 46% of patients were in treatment with inhaled glucocorticoids and, as in the work by Mancía, it was not found to influence the prognosis of patients with COPD.¹⁸ No differences were found in patients who were in chronic inhalation therapy with beta-adrenergics, tiotropium, or other long-acting anticholinergics either. The protective and prognostic role in COVID-19 of habitual inhalation therapy in patients with COPD is continuously under review. Indeed, there are works that do suggest benefits of tiotropium as a protective factor against SARS-CoV-2 infection¹⁹ and others in which inhalatory treatment with steroids and tiotropium are a protective factor against mortality.²⁰

The improvement in the prognosis of patients who received treatment with inhaled bronchodilators was notable. In patients with exacerbated COPD, beta-adrenergics and short-acting muscarinic antagonists are the basis of treatment. The fact that there were patients who did not receive bronchodilator treatment during hospitalization may be due to the high rates of contagion among healthcare personnel attributed to the use of nebulizers during the first wave. In patients with COPD hospitalized due to COVID-19, bronchodilator treatment must be administered unless it is contraindicated. It is recommended to avoid nebulizations and instead provide treatment with pressurized, dry powder, or soft mist inhalers with or without a spacer device.

Conclusions

Patients with COPD hospitalized due to COVID-19 are mainly men; older adults; have high comorbidity; and present with dyspnea, cough, fever or low-grade fever, and respiratory failure. In the second wave, patients presented with less respiratory failure and less radiological involvement. This better clinical condition, together with lesser healthcare overload and strain on hospitals and the updating of treatment protocols, may have been behind the lower mortality and better prognosis observed in the second wave.

Patients with COPD hospitalized due to COVID-19 must receive bronchodilator treatment unless it is contraindicated.

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Conflicts of interest

The authors confirm there are no conflicts of interest in the conduct of this work.

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Appendix A. List of SEMI-COVID-19 Network group members

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