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RESEARCH LETTER

Characterization of COPD Admissions During the First COVID-19 Outbreak

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Purpose: Exacerbations of COPD (ECOPD) are a frequent cause of hospitalization that seemed to ameliorate during the COVID outbreak. We aimed to evaluate the clinical characteristics of COPD-related hospital admissions and mortality in relation to the presence of COVID-19.

Patients and Methods: We conducted a case–control study of patients admitted in four teaching hospitals throughout Spain between March 15 and April 30, 2020. Hospital admissions of respiratory cause with and without PCR-proven SARS-CoV-2 infection in patients with COPD were evaluated. Baseline and episode-related clinical characteristics were analyzed. Logistic regression analysis was performed to evaluate the risk for mortality.

Results: During the study period, 2101 patients were admitted for respiratory worsening, 1200 (57.1%) with COVID-19. A total of 228 (10.8%) were admitted due to COPD worsening, of whom 52 (22.8%) tested positive for COVID-19. COPD patients with COVID-19, when compared to those without COVID-19, were more frequently males with better lung function (FEV_1 postbronchodilator 71% vs 46% respectively, $p<0.001$) and had higher mortality (44.9% vs 13.6% respectively, $p<0.001$) despite similar age, comorbidities, total days of hospitalization and admission to intensive care unit. COVID-19 and eosinopenia were the strongest risk factors for mortality in the multivariate analysis in the overall COPD population. Inhaled corticosteroid use was not associated to mortality.

Conclusion: Hospitalizations for ECOPD without COVID-19 were more frequent than COPD with COVID-19 during the first outbreak, but the latter were associated with higher mortality and low eosinophil counts that warrant further analysis.

Keywords: COPD exacerbation, mortality, inhaled corticosteroids, hospitalization

Introduction

Exacerbations of chronic obstructive pulmonary disease (ECOPD) are a frequent cause of hospital admissions that seem to be modified by COVID-19. Although many studies have shown that various comorbidities, including COPD, are associated with high severity and mortality among the COVID-19 population, little is known about the characteristics of the SARS-CoV-2 infected COPD patients compared to patients that require admission for a severe COPD exacerbation. Moreover, the specific impact of SARS-CoV-2 infection in hospitalized COPD patients is not yet well established. In addition, the potential protective role of inhaled therapies for an adverse outcome of COVID-19 in COPD patients is yet to be explored. In the current study, we aimed to investigate the clinical characteristics and the role of therapies in consecutive patients with COPD with a respiratory-related hospital admission in Spain during the first outbreak wave of the COVID-19 pandemic and to evaluate the presence of COVID-19 as a risk factor of mortality in this cohort.

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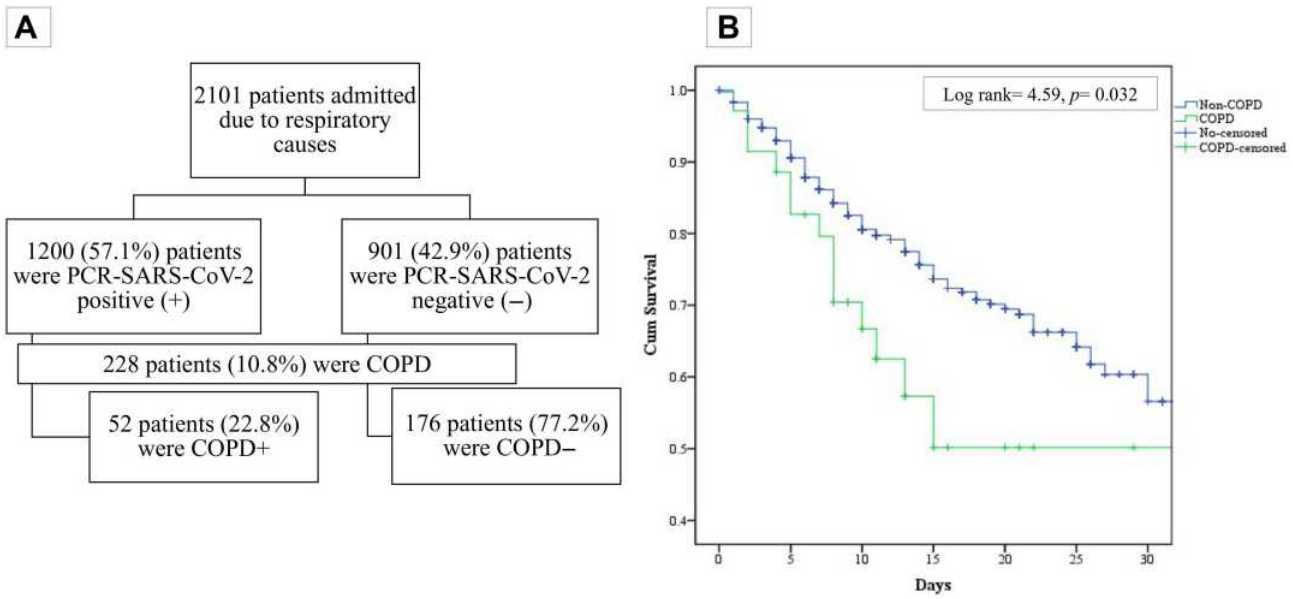

Figure 1 (**A**) Flow chart of the studied population. (**B**) Kaplan–Meier survival analysis of whole COVID-19 population in relation to the presence or absence of COPD as comorbidity.

Patients and Methods

We conducted a case–controlled study in four teaching hospitals between March 15 and April 30, 2020. All cases with COPD who were admitted to hospital due to any respiratory worsening were included. All the COPD patients enrolled in the current study had previous diagnosis of COPD according to GOLD criteria that was confirmed by postbronchodilator airflow limitation (FEV_1/FVC <0.7) using forced spirometry testing. COVID-19 was identified using a polymerase chain reaction test for SARS-CoV-2 in nasopharynx samples. Baseline and episode-related clinical characteristics of the enrolled patients were analyzed. Bivariate and multivariate logistic analysis were used to evaluate the risk factors for in-hospital mortality. Thirty-day in-hospital mortality was analyzed using Kaplan-Meier survival curve and log rank test among COVID-19 infected patients. The study was approved by the Research Board of Hospital Universitario Son Espases and the participating hospitals. Owing to the retrospective nature of the study informed consent was waived. We confirm that all patient data accessed complied with relevant data protection and privacy regulations, and that this study was conducted in accordance with the Declaration of Helsinki.

Results

Throughout the study duration, a total of 2101 patients were admitted for respiratory reasons in the participating hospitals, of which 1200 (57.1%) patients were PCR-SARS-CoV-2 positive. A total of 228 (10.8%) were admitted due to COPD worsening, of whom 52 (22.8%) tested positive for COVID-19 (Figure 1A). Baseline values revealed some differences between COPD cases positive for COVID-19 (COPD+) and COPD exacerbations without COVID-19 (COPD–). Both groups had similar mean age, comorbidities and smoking index. However, COPD+ were more frequently males (92.3% vs 80.7%, p=0.048; Table 1). Baseline treatments were similar for both groups except for LAMA monotherapy more frequent in COPD+ (13.5% vs 3.4%, p=0.028; Table 1) and oxygen therapy more frequent in COPD– (18.8% vs 5.8%, p=0.012; Table 1). Baseline post-bronchodilator FEV_1% predicted was significantly higher among COPD+ patients (71%; IQR=52.75–82.75 vs 46%; IQR=31–60, p<0.001; Table 1). C-reactive protein, D-dimer, lactate dehydrogenase and ferritin were significantly higher among COPD+ patients (p<0.05 for all comparisons; Table 1). Blood analysis revealed lymphopenia and eosinopenia, more pronounced for COPD+ cases (p<0.001 for both comparisons; Table 1).

Clinical outcomes showed some differences. Notably, in-hospital mortality was significantly higher among COPD with COVID-19 patients vs COPD patients without COVID-19 (44.9% vs 13.6% respectively; p<0.001). There was no statistically significant difference regarding total days of hospitalization (9.01±10.8 vs 11.5±8.2 days, p=0.220) or admission to intensive care unit (4.5% vs 5.8%, p=0.704; Table 1) between COPD+ and COPD–.

Table 1 Baseline and Laboratory Characteristics of the Hospitalized COPD Population (n=228, 10.8%) Classified According to Presence (COPD+) or Absence (COPD–) of COVID-19 Infection

Variable	COPD– (n=176; 77.2%)	COPD+ (n=52; 22.8%)	Sig. (*p*-value)
Age; mean ±SD	71.98±10.96	72.96±10.75	0.568
Male/female; (n, %)	142 (80.7)/34 (19.3)	48 (92.3)/4 (7.7)	0.048*
Smoking index (pack-years); mean ±SD	55.37±26.03	60.29±32.56	0.558
Co-morbidities; (n, %)	148 (84.1)	45 (86.5)	0.667
Days of hospitalization; mean ±SD	9.01±10.76	11.49±8.24	0.220
ICU admission; (n, %)	8 (4.5)	3 (5.8)	0.704
Medications; (n, %)			
LAMA	6 (3.4)	7 (13.5)	0.028*
LAMA/LABA	18 (10.2)	6 (11.5)	0.158
LABA/ICS	9 (5.1)	5 (9.6)	0.193
Triple therapy	42 (23.9)	6 (11.5)	0.110
Roflumilast	6 (3.4)	0 (0)	0.195
Baseline oxygen therapy	33 (18.8)	3 (5.8)	0.012*
Baseline NIV	14 (8)	0 (0)	0.113
Baseline spirometry:			
FEV_1% predicted	46 (31–60)	71 (52.75–82.75)	<0.001*
FEV_1 (mL)	1170 (910–1650)	1745 (922.5–2300)	0.004*
FEV_1/FVC	44 (36–58)	60 (43.5–67)	0.028*
Laboratory data:			
WBC (cells/uL)	9830 (7432.5–13425)	7460 (5660–10200)	<0.001*
Lymphocytes (cells/uL)	1250 (822.5–1895.0)	830 (630–1200)	<0.001*
Neutrophils (cells/uL)	7780 (5312.5–11402.5)	5800 (3875–8085)	0.007*
Eosinophils (cells/uL)	80 (30.0–177.5)	20 (0.0–70.0)	<0.001*
LDH (U/L)	193 (155.75–287.0)	328 (267.25–475.75)	<0.001*
Ferritin (ng/mL)	191 (92.0–646.5)	776 (340.5–1729.0)	0.003*
D-dimer (ng/mL)	406 (199–1026)	785 (397.25–2354.25)	0.021*
CRP (mg/L)	4.42 (0.45–22.69)	28.84 (10.97–69.5)	<0.001*
Advanced treatment for COVID-19			
NIV; (n, %)	22 (12.5)	2 (3.8)	0.02*
MV; (n, %)	3 (1.7)	2 (3.8)	0.497
ECMO; (n, %)	1 (0.6)	0 (0)	0.628

Notes: Data are presented as median (interquartile range) unless otherwise stated. Statistics: χ^2 test, Mann–Whitney and Student's *t*-tests were used as appropriate. *Significant *p*-value <0.05

Abbreviations: COPD–, COPD with negative PCR-SARS-CoV-2; COPD+, COPD with positive PCR-SARS-CoV-2; SD, standard deviation; n, number; ICU, intensive care unit; LAMA, long-acting muscarinic antagonist; LABA, long-acting beta 2 agonist; ICS, inhaled corticosteroid; NIV, noninvasive ventilation; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; mL, milliliter; WBC, white blood count; LDH, Lactic acid dehydrogenase; CRP, C-reactive protein; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

When only COVID-19 patients were assessed, Kaplan–Meier survival analysis showed that COPD+ patients had worse survival compared to those without COPD (50% vs 60% respectively, p=0.032; Figure 1B).

Moreover, patients with COPD were at 2.8-fold higher risk of in-hospital mortality in COVID-19 population (95%CI=1.5–5.3, p=0.002) after correction for age, gender and other comorbidities despite being less likely to acquire COVID-19 disease (COPD+: 52/228 (22.8%) vs non-COPD with COVID-19: 1148/1873 (61.3%); odds ratio (OR)= 0.19, 95%CI=0.14–0.26, p<0.001). It is noteworthy that treatment with inhaled corticosteroids (ICS) showed

Table 2 Multivariate Logistic Analysis of the Predictors of Mortality Among Whole COPD Population

	OR	95%CI for OR		Sig. (p-value)
		Lower	Upper	
Age	1.89	0.86	4.19	0.116
Male gender	3.18	0.35	28.95	0.304
Comorbidities other than respiratory	1.23	0.18	8.53	0.835
COVID-19 infection	4.99	1.30	19.17	0.019*
D-dimer	1.27	0.81	1.97	0.300
CRP	1.14	0.74	1.75	0.548
Eosinopenia	2.11	1.08	4.16	0.030*
WBC	1.12	0.66	1.90	0.673
Lymphopenia	1.52	0.87	2.65	0.141
Intercept	0.002			0.005*

Note: *Significant *p*-value <0.05.
Abbreviations: OR, odds ratio; CI, confidence interval.

a nonstatistically significant effect on mortality (OR=0.75, 95%CI=0.24–2.33, *p*=0.619) or acquiring COVID-19 among COPD patients (OR=0.48, 95%CI=0.18–1.28, *p*=0.141).

Further, we found in multivariate logistic regression for mortality that COVID-19 and eosinopenia were the main determinants of in-hospital mortality after correction for age, gender, comorbidities and laboratory tests of interest (OR=4.99, 95%CI=1.3–19.17, *p*=0.019 and OR=2.11, 95%CI=1.08–4.16, *p*=0.03 respectively; Table 2) in COPD patients.

Discussion

As shown in the current analysis, COPD patients infected with COVID-19 had higher mortality than COPD patients admitted for other cause of exacerbations. Interestingly, despite the higher mortality they showed less severe disease than COPD–, with milder airflow limitation, less intensive treatment for COPD and similar comorbidities. The reason for the increased risk of death is unclear but seems directly attributed to SARS-CoV-2 infection and their complications. Higher expression of angiotensin-converting enzyme 2 (ACE-2) receptor in the bronchial epithelium of COPD and smokers that facilitates the binding of SARS-CoV-2 to cells leading to infection[1] could be an explanation of the severity of COVID-19 disease among COPD patients irrespective of the severity of underlying disease. A limited access to more advanced treatments such as noninvasive ventilation or ICU admission was not observed in our series. Gómez-Antúnez et al similarly found that neither noninvasive ventilation, high-flow nasal cannula or invasive mechanical ventilation were associated with better survival among COPD infected with COVID-19.[2]

In line with our finding, a meta-analysis showed that COPD patients are at high risk for more severe COVID-19 disease and higher mortality compared to non-COPD patients.[3] However, to our knowledge, the majority of the studies compared COPD and non-COPD patients hospitalized for COVID-19 rather than COPD admitted due to other causes. On the contrary, other reports did not list COPD as a comorbidity associated to mortality in their COVID-19 series.[4,5]

In addition, in the current analysis we found that COPD patients with more severe disease had less chance of acquiring SARS-CoV-2 infection which could be due to less active daily life, feeling compelled to self-isolat e because of fear of dying from COVID-19, more adherence to medications and satisfaction with medical telephone visits.[6,7]

Alternatively, we showed a lower prevalence of COVID-19 among COPD population. This finding is in accordance with Gómez-Antúnez et al[2] who reported low prevalence of COPD among their analyzed 10,420 patients (7.16%). Guan et al in China found that COPD constituted 1.3% of COVID-19 cases,[8] while Cummings et al in New York City reported that COPD and interstitial lung diseases constituted 9% of their COVID-19 cases.[9] Alqahtani et al[3] in their systematic review and meta-analysis found that 2% only of COVID-19 patients were COPD. Interestingly, previous reports showed that neither MERS-CoV nor SARS-CoV-1 were associated with COPD exacerbation in contrast to other coronaviruses such as OCA3 and 229E.[10] The exact cause is still unclear, but the use of inhaled steroids, beta-agonists or anticholinergics[11] could be implicated through inhibition of the expression of coronavirus receptors, reduction of endosomal activity[11] and modulation of the airway inflammatory response to coronavirus infection.[12]

Interestingly, ICS in the current analysis did not have a statistically significant protective effect against the development of COVID-19 among the COPD population or mortality in the bivariate or multivariate regression analysis. Despite that ICS use has a proven protective

effect against exacerbations among frequent-exacerbator COPD patients, to date, there is no conclusive data supporting that ICS use is associated with reducing or increasing the risk of COVID-19 among COPD population. Schultze et al found that ICS did not provide a protection against severe COVID-19 infection in COPD patients but could be associated with overall increased risk of mortality.[13] Choi et al, in another epidemiological study performed in Korea, found that ICS users had higher in-hospital mortality rates, but this association was not significant when adjusted for various confounding factors.[14] On the contrary, a recent study showed that ICS and biological therapy in asthmatics may have a protective effect against the development of severe COVID-19.[15]

Lastly, COVID-19 and eosinopenia were the main determinants of in-hospital mortality in multivariate logistic analysis. Yang et al found that high blood eosinophils were associated with significant lower in-hospital mortality among critically ill patients admitted to hospital due to severe ECOPD.[16] This could be explained based on a good response to systemic corticosteroids given in the management of ECOPD, especially if eosinophilic COPD phenotype. Furthermore, it has been previously reported that low eosinophils in peripheral blood is associated with potentially pathogenic bacterial infection[17] and worse outcomes of ECOPD. Yan et al also found in 109 COVID-19 patients that progressive decline of eosinophilic count is linked to tissue damage and mortality.[18]

Study Limitations

The current study had some limitations. Firstly, we did not analyze the cause of COPD of the studied population; however, the main cause of COPD is smoking while a percentage is still caused by biomass population. Secondly, we did not investigate the prehospital use of systemic corticosteroids as risk factor of COVID-19 mortality among our COPD population. Choi et al[14] and Williamson et al[19] found that the use of systemic corticosteroids for COPD and asthma in the year prior to inclusion in the study was associated with significant increased risk of COVID-19 related mortality. Lastly, we could not compare the rate of exacerbation with those in preceding years; however, our aim was to compare them with COVID-19 in COPD patients.

Conclusions

Hospitalizations for ECOPD without COVID-19 were more frequent than COPD with COVID-19 during the first pandemic wave, but the latter were associated with higher mortality. The association of low eosinophil counts with higher mortality in the COPD with COVID-19 warrants further analysis. We found no evidence to support the role of ICS as protective factor for mortality due to SARS-CoV-2 infection among COPD patients.

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Disclosure

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