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ORIGINAL RESEARCH

Persistent Respiratory Failure and Re-Admission in Patients with Chronic Obstructive Pulmonary Disease Following Hospitalization for COVID-19

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Background: Chronic obstructive pulmonary disease (COPD) has been associated with worse clinical evolution/survival during a hospitalization for SARS-CoV2 (COVID-19). The objective of this study was to learn the situation of these patients at discharge as well as the risk of re-admission/mortality in the following 12 months.

Methods: We carried out a subanalysis of the RECOVID registry. A multicenter, observational study that retrospectively collected data on severe acute COVID-19 episodes and follow-up visits for up to a year in survivors. The data collection protocol includes general demographic data, smoking, comorbidities, pharmacological treatment, infection severity, complications during hospitalization and required treatment. At discharge, resting oxygen saturation (SpO2), dyspnea according to the mMRC (modified Medical Research Council) scale and long-term oxygen therapy prescription were recorded. The follow-up database included the clinical management visits at 6 and 12 months, where re-admission and mortality were recorded.

Results: A total of 2047 patients were included (5.6% had a COPD diagnosis). At discharge, patients with COPD had greater dyspnea and a greater need for prescription home oxygen. After adjusting for age, sex and Charlson comorbidity index, patients with COPD had a greater risk of hospital re-admission due to respiratory causes (HR 2.57 [1.35–4.89], p = 0.004), with no significant differences in survival.

Conclusion: Patients with COPD who overcome a serious SARS-CoV2 infection show a worse clinical situation at discharge and a greater risk of re-admission for respiratory causes.

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Introduction

The disease caused by the SARS-CoV2 virus (COVID-19) has had a major impact worldwide due to its high morbidity and mortality. Advanced age, active smoking and the presence of comorbidities like chronic obstructive pulmonary disease (COPD) have been associated with worse clinical evolution or survival.[1–7] The up-regulation of the angiotensin converting enzyme-2 (ACE-2) receptor, impaired innate and adaptive immune responses and demonstrated delayed clearance of respiratory viruses in these patients are some of the proposed mechanisms.[7] Together, these factors may facilitate the propagation of SARS-CoV-2 in the lungs of patients with COPD, leading to rapid clinical deterioration and progression to severe COVID-19.[7] Furthermore, COPD itself can act as a risk factor for re-admission and worse survival following hospitalization for COVID-19.[8–10] However, limited studies have been conducted specifically in this population. The objective of this study was to learn the situation of patients with COPD at discharge as well as the risk of re-admission and mortality following hospitalization for SARS-CoV2 infection.

Methods

For the study, we carried out a subanalysis of the RECOVID (Spanish Registry for Hospitalized COVID-19) registry at 49 Spanish hospitals with patients hospitalized in 2020 (March–November) with a confirmed SARS-CoV2 infection using SARS-CoV2 RT-PCR.[11] Briefly, it is a multicenter, observational study that retrospectively collected data on acute COVID-19 episodes and follow-up visits for up to a year in survivors. Patients with COVID-19 registered in the pneumology service of each participating center (stratum) were identified. To achieve a more representative cohort of patients, including different geographical areas, each center recruited groups of 50 randomly selected patients before entering the data. Only three hospitals recruited consecutive patients. The study was approved by both the Ethics Committee (Comité Ètic d'Investigació Clínica, Hospital San Pau, Barcelona) on 29 April 2020 and by the local committees of the participating centers. An electronic database was created and stored on the XOLOMON web platform to gather anonymized data in accordance with regulation (EU) 2016/679 of the European Parliament and of the Council, of 27 April 2016, and Spanish Organic Law 3/2018. The data collection protocol includes general demographic data, smoking, comorbidities, pharmacological treatment, infection severity, complications during hospitalization and required treatment. At discharge, resting oxygen saturation (SpO2), dyspnea according to the mMRC (modified Medical Research Council) scale and long-term oxygen therapy prescription were recorded. The follow-up database comprised clinical check-up visit data at 6 and 12 months, including information related to symptoms, analytical variables and complementary explorations, where re-admission and mortality were recorded. The study used a data monitor to review inconsistencies and missing data and prepare follow-up questions for each hospital. To deem each case valid, a minimum of 70% of completed data regarding the fundamental variables was necessary. After being evaluated by the ethics committee, informed consent was not required to carry out this study.

For the statistical analysis of qualitative variables, frequencies (and percentage) were calculated, while average and standard deviation were used for quantitative variables. Follow-up time was summarized using the median and maximum. Charlson index values were compared using independent mean contrast. The association between qualitative variables and the presence of COPD was evaluated using the chi-square test of independence. To compare the survival curves for the post-discharge death and re-admission variables, the Kaplan-Meier Log rank test was used. A Cox regression analysis was carried out to evaluate the impact of COPD on mortality and re-admission, after adjusting for age, sex and Charlson index, and before verifying the risk proportionality assumption. To analyze the risk of re-admission due to respiratory causes, the analysis was also adjusted for current smoking or pack-year index. All analyses were carried out with R software, version 4.2.1.[12]

Results

2047 patients were included (March–November 2020), of which 115 (5.6%) had been diagnosed with COPD. The characteristics of both groups are described in Table 1. Patients with COPD were older, had a greater smoking history and a greater comorbidity burden compared to patients without COPD. At discharge, patients with COPD had greater dyspnea, a lower baseline SpO2 and a greater need for prescription home oxygen (13.1% vs 5.3%, p = 0.007).

Table 1 Baseline Characteristics of Patients Included in the Study

Variables	No COPD (N_1=1932)	COPD (N_2=115)	p
Age, N_1=1924 and N_2=115	61(51–71)	71.9±8.9	<0.001
Women, N_1=1918	796(41.5)	21(18.3)	<0.001
Pack-year index, N_1=1549 and N_2=76	5.08±16.71	37.67±28.11	<0.001
Body mass index, N_1=965 and N_2=76	29.0±5.7	29.3±5.1	0.818
Smoking history, N_1=1879 and N_2=111			
Never smoker	1269(67.5)	10(9)	<0.001
Former smoker	525(27.9)	88(79.3)	<0.001
Current smoker	85(4.5)	13(11.7)	0.001
ICU admission required, N_1=1918 and N_2=111	367(19.5)	14(13)	0.118
Orotracheal intubation required, N_1=1918 and N_2=113	283(14.8)	11(9.7)	0.181
Dyspnea at discharge (mMRC), N_1=1228 and N_2=88			
0	560(45.6)	30(34.1)	0.047
1	446(36.3)	16(18.2)	<0.001
2	183(14.9)	29(33)	<0.001
3	32(2.6)	13(14.8)	<0.001
4	7(0.6)	0(0)	1
Baseline oxygen saturation at discharge, N_1=1558 and N_2=91	95.4±6.4	93.5±3.1	<0.001
New home oxygen prescription at discharge, N_1=1562 and N_2=84	83(5.3)	11(13.1)	0.007
Charlson comorbidity index score	0.89±1.47	3.08±2.38	<0.001
Comorbidities, N_1=1929 and N_2=114			
Previous myocardial infarction	83(4.3)	13(11.3)	0.001
Congestive heart failure	46(2.4)	13(11.3)	<0.001
Peripheral artery disease	61(3.2)	14(12.3)	<0.001
Cerebrovascular disease	64(3.3)	14(12.3)	<0.001
Dementia	65(3.4)	2(1.8)	0.584
Rheumatic disease	78(4.1)	16(13.9)	<0.001
Peptic ulcer	39(2)	5(4.3)	0.098
Mild liver disease	46(2.4)	6(5.2)	0.069

(*Continued*)

Table 1 (Continued).

Variables	No COPD (N$_1$=1932)	COPD (N$_2$=115)	p
Diabetes mellitus	313(16.3)	39(33.9)	<0.001
Cerebrovascular event	17(0.9)	4(3.5)	0.027
Moderate to severe kidney disease	89(4.6)	11(9.6)	0.029
Diabetes with chronic complications	31(1.6)	12(10.4)	<0.001
Cancer without metastasis	118(6.1)	18(15.7)	<0.001
Leukemia	9(0.5)	0(0)	1
Lymphoma	13(0.7)	0(0)	1
Moderate or severe liver disease	36(1.9)	6(5.2)	0.028
Solid metastatic tumor	12(0.6)	2(1.7)	0.186
Asthma	151(7.8)	8(7)	0.871
Obstructive sleep apnea	117(6.2)	24(20.9)	<0.001

The average length of follow-up was 379 days (378 days for the patient cohort without COPD and 382 for the COPD cohort). A total of 191 patients (8.5%) had to be re-hospitalized (164 (8.5%) in the non-COPD group and 27 (23.5%) in the COPD group, p < 0.001). Compared to patients without COPD, patients with COPD showed a greater need to be re-admitted for any cause (χ^2 = 29.9, df = 1, p < 0.001, Figure 1A), for respiratory causes (χ^2 = 33.7, df = 1, p < 0.001, Figure 1B) and for cardiovascular causes (χ^2 = 10, df = 1, p = 0.001, Figure 1C), without finding any differences with respect to re-admission for other causes (χ^2 = 1, df = 1, p = 0.30, Figure 1D). In the Cox multivariate analysis adjusted for age, sex and Charlson comorbidity index, patients with COPD were found to have a greater risk of hospital re-admission for respiratory causes (HR 2.57 [1.35–4.89], p = 0.004). This high risk remained after adjusting for current smoking or pack-year index (HR 2.48 [1.28–4.8], p = 0.007 and HR 4.2 [1.8–9.8], p = 0.001, respectively). The risk of re-admission for any cause, for cardiovascular causes or other causes was not statistically significant (HR 1.48 [0.95–2.32], p = 0.084; HR 1.5 [0.55–4.0], p = 0.443 and HR 0.84 [0.36–1.96], p = 0.69, respectively) after adjusting for age, sex and Charlson comorbidity index.

Seventy patients passed away during follow-up. In the 12 months following discharge, 8.5% of patients with COPD and 2.7% of patients without COPD had passed away (p < 0.001). Although the group of patients with COPD showed worse survival compared to patients without COPD in the crude analysis (χ^2 = 10.5, df = 1, p = 0.001), in the multivariate analysis adjusted for sex, age and Charlson index, the impact of COPD on survival was not significant (HR 0.89 [0.41–1.93], p = 0.76).

Discussion

Our study has two relevant conclusions: 1) patients with COPD who overcome severe SARS-CoV2 infection have a worse clinical situation at discharge; 2) patients with COPD have a greater risk of re-admission, especially for respiratory causes. Studies conducted in the early stages of the COVID-19 pandemic showed that patients with COPD were hospitalized with a worse clinical situation, had high comorbidity (especially cardiovascular) and worse survival.[13] Our study identifies hospitalized patients with COPD that overcome viral infection as a more vulnerable group and, consequently, at greater risk of suffering worse evolution after discharge. The baseline situation of patients with COPD, the severity of the process, prolonged stay, the treatment used, the presence of comorbidities, and SARS-CoV2 variant are some of the factors that will influence a patient's situation when the infection resolves.[1–6,14] Furthermore, COPD exacerbation due to SARS-COV2 seems to have a worse prognosis compared to other exacerbations not related to this
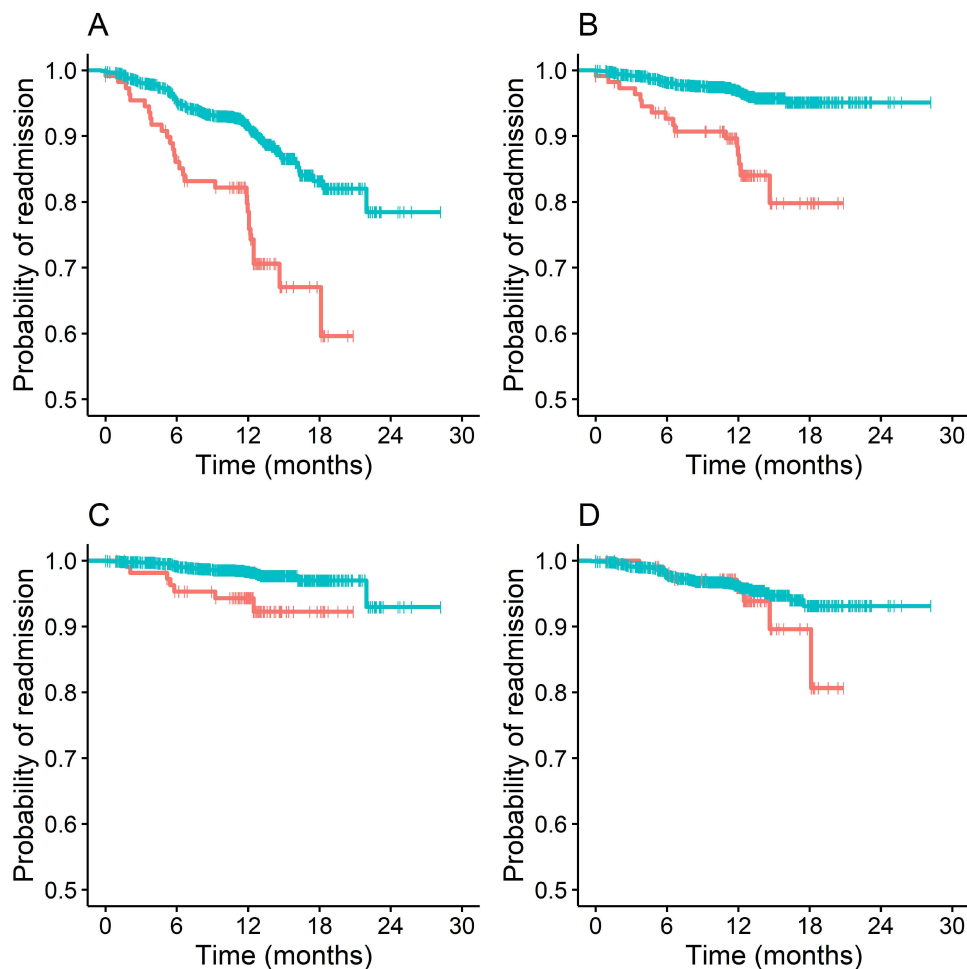
Figure 1 Re-admissions over the follow-up period. Re-admissions for any cause (**A**), respiratory causes (**B**), cardiovascular causes (**C**) or any other cause (**D**). Red line: COPD patients; Blue line: Non-COPD patients.

virus. Hyams et al[14] compared outcomes of patients hospitalized with SARS-CoV-2 infective exacerbation vs non-SARS-CoV-2 infective exacerbation and found that SARS-CoV-2 exacerbation was associated with worse outcomes than for those admitted with non-SARS-CoV2 infective exacerbation, with a 55% and 26% and 35% increased risk of positive pressure support, hospitalization length and 30-day mortality, respectively, when controlling for potential confounders such as age, chronic medical conditions and vaccination status.

The rate of re-admission in the 12 months following hospitalization for COVID-19 is estimated to be ≈ 10%,[15,16] being higher in the elderly and in subjects with multiple comorbidities like COPD or cardiovascular disease.[8–10] In our study, the probability of re-admission for patients with COPD was almost triple that of patients without COPD (24.1% versus 8.6). The presence of cardiovascular comorbidities combined with advanced age along with the respiratory disease itself could have a synergistic effect that would negatively affect these patients' evolution. With respect to causes of re-admission, a meta-analysis by Akbari et al[8] found respiratory and cardiac complications to be the main causes (48% and 14%, respectively): respiratory sepsis, COVID-19, pneumonia and the presence of pulmonary thromboembolism were the main diagnoses,[10,16,17] situations in which patients with COPD are especially vulnerable.[18–20] In our study, mortality at one year in patients with COPD was higher than patients without COPD, a result that coincides with previous studies.[21] However, variability in the percentage of deaths in different studies may be a reflection of the heterogeneity of the populations analyzed, the inclusion criteria used, the follow-up policies or the level of severity at hospitalization.[15] Data obtained from large databases such as Medicare shows that, in patients who were discharged alive from a COVID-19 related hospital admission (between March 2020 and August 2022), the risk of post-discharge death was nearly two-

fold compared to the influenza virus, with most of the difference occurring within 30 days of discharge. These findings emphasize the need for patients who overcome a severe SARS-CoV2 infection to be monitored closely after discharge.[22]

Among the strengths of this study, we can highlight the large sample size and its multicentric nature. To our knowledge, this is the first study to analyze the evolution of patients with COPD following hospitalization for COVID-19. The limitations are those inherent to retrospective registries, with different diagnostic and follow-up protocols at the different hospitals. It is possible that the pandemic caused difficulties in out-patient follow-up,[23] which could influence the high rate of re-admission in these patients with a more precarious clinical situation at discharge. In addition, our study was carried out at a time when vaccination against the SARS-COV2 virus had not yet been implemented. Current evidence suggesting that outcomes have improved over time for patients with COPD hospitalized with SARS-CoV-2 based on circulating and dominant variants, vaccination rates, healthcare pressure and COVID-19 treatments is varied.[14,22,24–28] Taking into account these aspects, more studies will be required to confirm our results in the current health situation, especially with regard to these patients' evolution after hospital discharge, evaluating the clinical impact of new dominant SARS-CoV2 variants, treatments and vaccination on this group of patients.

In conclusion, patients with COPD who have overcome severe SARS-CoV2 infection have a high risk of re-admission, especially re-admission related to respiratory causes, and show greater clinical deterioration at discharge, requiring oxygen for persistent respiratory distress, which could point to the need to create specific follow-up plans in this specific patient group.

Ethics and Consent Statements

The study was approved by both the Ethics Committee (Comité Ètic d'Investigació Clínica, Hospital San Pau, Barcelona) on 29 April 2020 and by the local committees of the participating centers. The study did not require informed consent.

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