Pneumonia

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Organizing pneumonia in hospitalized COVID-19 patients: risk factors and long-term outcomes

Sandra Cuerpo[1], Fernanda Hernandez-Gonzalez[2], Mariana Benegas[3], Nuria Albacar[2], Alejandra Lopez-Giraldo[4], Inés Cobo[2], Samara Suarez[3], Verónica Torres[3], Adelaido Salazar[6], Nestor Soler[3], María Noboa-Sevilla[3], Alejandro Frino-García[3], Nancy Pérez-Rodas[3], Joel Francesqui[7], Xavier Alsina-Restoy[3], Ana María Muñoz Fernández[8], Nuria Roger[8], Sergio Prieto[6], Alexandru Vlagea[9], Estibaliz Ruiz[9], Rosa Faner[10,11,12], Joan Albert Barberà[3,10,11], Alex Soriano[13], Joan Ramon Badia[3], María Molina-Molina[11,14], Oriol Sibila[3,10,11], Marcelo Sánchez[4], Alvar Agustí[2,10,11,15†], Judith Garcia-Aymerich[5†] and Jacobo Sellares[2,10,11,16*†]

Abstract

Background Some patients develop post-COVID-19 organizing pneumonia (OP) that is responsive to corticosteroid treatment. This multicenter, case-control study of patients hospitalized for COVID-19 sought to determine the prevalence, risk factors, radiological outcomes, and evolution after treatment.

Methods We included 153 consecutive patients with OP and 140 without OP who required hospitalization because of COVID-19 from February to April 2020. OP patients were followed up for 12 months, with visits at 1, 3, 6, and 12 months after hospital discharge.

Results Risk factors for OP at hospital admission were advanced age, previous respiratory disease, and elevated C-reactive protein levels. Follow-up computed thoracic (CT) scans performed one year after admission showed progressive improvement in radiological involvement; however, up to 57% of patients with OP remained with fibrotic-like changes. Multivariate analysis showed a significant association of fibrotic pattern with older age, high dose of corticosteroids, and extensive parenchymal lung involvement on admission CT scans.

Conclusions Following COVID-19 OP, fibrotic-like changes may persist over the long term. Higher dose of corticosteroids does not seem to be associated with a better prognosis.

Keywords COVID-19, Organizing pneumonia, Corticosteroids

†Alvar Agustí, Judith Garcia-Aymerich and Jacobo Sellares contributed equally as co-senior authors.

*Correspondence:
Jacobo Sellares
sellares@clinic.cat

Full list of author information is available at the end of the article

Introduction

Some patients may develop interstitial lung disease (ILD) because of COVID-19 infection. The most prevalent radiological pattern detected in chest-computed tomography (CT) is organizing pneumonia (OP) characterized by ground glass opacification (GGO), consolidation and septal thickening [1, 2]. Previous studies have reported that 12,5% of COVID-19 hospitalized patients may develop OP [3]. Older age and acute illness severity were identified as risk factors for development of ILD post COVID-19 [4].

It has been reported that approximately one-third of these OP-like cases present complete radiographic resolution of pulmonary lesions 1–2 months after hospitalization. In contrast, other patients eventually develop fibrotic-like changes [5] likely related to persistent inflammation, as shown in a *post-mortem* lung tissue analysis by our group [6].

Given that organizing pneumonia is known to be steroid responsive and is the most common radiological pattern during acute and follow-up scans, much interest has been invested in corticosteroid treatment, although results from previous studies are contradictory.

The objectives of this study are: *(1)* identify risk factors for the development of OP pattern during the acute phase of COVID-19 and *(2)* describe the natural history of OP one-year post-discharge follow-up, including the potential effect of oral corticosteroid treatment.

Methods

Study design, population and ethics

This was a multicenter, case-control study with a prospective follow-up of 12 months after hospital discharge and visits at 1, 3, 6, and 12 months after discharge. Cases ($n = 153$) were defined as patients hospitalized due to COVID-19 infection who tested positive on nasal swabs from March to April 2020 in three university hospitals in Catalonia, Spain (Clínic Barcelona, Bellvitge Hospital, and Vic Hospital) that developed OP pattern in CT after 14 days of symptoms onset. We excluded patients with interstitial pathology that could be due to other causes such as coinfection by other germs demonstrated in microbiological cultures, although since the study was carried out in the first wave of the pandemic it was not possible, due to the risk involved, performing fibrobronchoscopy or taking biopsies. We also excluded immunocompromised patients (HIV, neoplastic disease or immunosuppressive drugs).

To investigate the risk factors for OP during hospitalization, we generated a control population ($n = 140$) from a random sample of COVID-19 patients admitted to the same hospitals in the same period who, at day 14 after the onset of symptoms, had improvement or disappearance of pulmonary opacities on chest radiography and followed a favorable evolutionary course without requiring in any case ventilatory support or admission to the ICU. The study protocol was approved by the Ethical Review Board of the coordinating hospital (HCB/2020/0410) and all patients provided informed consent.

Characterization of patients

The demographic, clinical, imaging and biological characteristics of the patients and controls were obtained from their electronic medical records. These data included age, sex, smoking status, body temperature, comorbidities (arterial hypertension, any chronic cardiovascular disease, any chronic respiratory disease, diabetes), inflammatory and metabolic parameters (ferritin, D-dimer, LDH, procalcitonin, lymphocyte count, C-reactive protein, and lactate dehydrogenase), and arterial blood gases (SaO_2, PaO_2 (FIO_2), and $PaCO_2$) at hospital admission and discharge. We also collected information on the following events: time from onset of symptoms to hospital admission, length of hospital stays, treatment (dose and duration) with azithromycin, antivirals (lopinavir/ritonavir, remdesivir), anti-inflammatory drugs (tocilizumab, anakinra, hydroxychloroquine), and/or oral corticosteroids. After discharge, FEV_1, FVC, and DLco were measured only in OP-like pattern cases at three, six and 12 months, and CT thorax scans after one and 12 months (see below), following international standards. The reference values were those of Roca et al. [7, 8].

Chest CT

For optimal diagnostic performance of computed tomography, images were obtained in deep inspiration, with thin sections (1 mm) and high spatial resolution reconstruction (HRCT). The images were taken on different equipment all of them Siemens which were renewed after pandemic. All chest CT images were independently reviewed by two thoracic radiologists (MB and MS with 7 and 17 years of experience respectively) and a pneumologist (SC). Before scoring, each observer underwent supervised training to score the HRCT patterns described below. The observers had no knowledge of the pulmonary function or other clinical indicators of disease severity. When there was a discrepancy, the final result was reached through consensus. Radiological findings included ground glass, opacities, consolidation, reticulation, traction bronchiectasis, subpleural bands, honeycombing, and pleural retraction [9, 10]. An OP-like pattern was defined as peri-bronchovascular consolidations with perilobular distribution and/or the reverse halo sign [10]. Fibrotic-like changes were defined as the presence of traction bronchiectasis, pleural retraction, parenchymal bands and/or honeycombing [11]. A CT score [12] was used to quantify parenchymal abnormalities when OP was suspected, one month and one year after

discharge. Both lungs were divided into their respective lobes. Involvement in each lobe was scored based on the following criteria: 0 (no involvement); 1 (< 10% involvement), 2 (10–25% involvement), 3 (25–50% involvement), 4 (50–75% involvement) and 5 (> 75% involvement). CT pulmonary angiography was performed when the blood D-dimer level was > 500 ng/ml, following the COVID-19 protocol from each hospital.

Statistical analysis

For continuous variables, descriptive statistics included n, proportion, mean ± SD, or median [25th-75th quartile]. We also compared the evolution of biological parameters between admission and hospital discharge in both cases and controls using Wilcoxon or McNemar paired tests. To investigate the risk factors for the development of OP-like pattern during hospitalization, we first compared clinical, biological, and radiological characteristics at admission between cases and controls using Student's, Mann-Whitney *U*, chi-square, or Fisher's exact tests as appropriate. We then built a multivariable logistic regression model that included all factors significantly different in this bivariate analysis. We used forward/backward strategies to obtain the most parsimonious model that explains the observations. Medical treatments were not included as potential risk factors, as they occurred during admission but not at baseline. To study the longitudinal evolution of OP patients, we assessed the distribution of radiological (at 1 and 12 months) and functional (at 3, 6, and 12 months) characteristics using univariate statistics and their changes over time using paired tests. Finally, we determined the factors at hospital discharge that predicted the persistence of fibrotic changes at one-year follow-up in OP patients using multivariable logistic regression (conditional stepwise forward model (Pin < 0.10, Pout < 0.05). Receiver operating characteristic (ROC) curves were used to determine the optimal cutoff values of daily corticosteroid dose in relation to the persistence of fibrotic changes. These cutoff values were included in the multivariate analysis. All analyses were performed using Stata 16.0 (StataCorp, College Station, TX, USA) and SPSS 26.0 (SPSS Inc., Chicago, IL, USA).

Results

Hospital admission

At hospital admission, patients with OP-like pattern were older, more frequently male, had more frequent comorbidities among them 29 had lung pathologies (55% COPD, 17% asthma, 14% bronchiectasis and 14% SAHS), and showed higher D-dimer and C-reactive protein levels and lower lymphocyte counts than patients in the control group (Table 1). No differences were observed in arterial blood gas levels at admission.

Patients in the OP-like pattern group had a more extended hospitalization period than the control group (an average of 19 days in OP group compared to 9 days in the control group); 64 (42%) were admitted to the ICU during hospital stay; 31 (20%) were intubated and mechanically ventilated, 2 (1%) received non-invasive ventilation, and 51 (33%) received high flow nasal cannula (HFNC) therapy. During hospitalization, most patients in the OP-like pattern group (86,9%) received corticosteroid therapy (mean dose of prednisone: 2132/-1196 mg/day), the duration and dose of corticosteroid depended on the decision of the physician who treated the patients. Side effects detected during admission and follow-up visits included weight gain (10 patients,6.5%), hyperglycemia (9 patients, 5.8%), maniac episodes (1 patient,0.6%), voice dysfunction (1 patient,0.6%), osteoporotic fracture (1 patient,0.6%), and distal tremor (1 patient,0.6%). None of the patients in the control group received corticosteroids.

Supplemental Table 1 compares oxygenation and analytical parameters between admission and the date of OP diagnosis. Patients with OP-like pattern required a higher FiO_2, have lower C-reactive protein levels and higher D-dimer levels. Despite this increase in D-dimer, pulmonary embolism was detected in only 13 (8%) patients.

Figure 1 shows a significant reduction in ferritin, LDH and D-dimer at discharge in OP-like pattern patients compared to controls. Hospital and one-year mortality in the OP group were 4.6% ($n = 7$) and 5.2% ($n = 8$), respectively.

Risk factors for the development of OP-like pattern during hospitalization

A mutually adjusted multivariable logistic regression showed that being older (adjusted odds ratio (OR) 1.03, 95% confidence interval [CI 1.01–1.055], $p = 0.005$), having a previous respiratory disease (OR 3.09, 95% [CI 1.35–7.78], $p = 0.011$), and higher levels of C-reactive protein (OR 1.04, 95% [CI 1.01–7.08], $p = 0.015$) at hospital admission were independent risk factors of developing OP-like pattern.

Long-term imaging follow-up

A chest CT scan was obtained in the OP-like pattern group when it was diagnosed during hospitalization and one month ($n = 130$, 85%) and one year after discharge ($n = 107$, 70%) (Fig. 2) (Table 2). During the follow-up period, CT scans showed progressive improvement with a reduction in ground glass opacities, consolidation, traction bronchiectasis, reticulation, and an improvement in the lung CT score in all lung lobes (Table 2). However, one year after the COVID-19 infection, 61 OP patients (57%) still presented with fibrosis-like changes.

Table 1 Clinical, biological and radiological characteristics at and during admission of COVID-19 patients with and without organizing pneumonia

	Control	*N* (total = 140)	OP	*N* (total = 153)	*p*-value
Age	58.3±15.2	140	64.6±12.8	153	0.001
Sex (female)	49(35%)	140	42(27.5%)	153	0.001
Temperature	37.3[36.5–38]	137	36.8[36.1–37.8]	151	0.04
Smoking		140		153	0.19
Non smoker	104(74.3%)		104(68%)		
Smoker	7(5%)		7(4.6%)		
Former smoker	9(6.4%)		2(1.3%)		
Arteria hypertension	5(3.6%)	140	5(3.3%)	153	0.01
Cardiopathy	14(10%)	140	7(4.6%)	153	0.001
Respiratory disease	11(7.9%)	140	29(19%)	153	0.001
Diabetes mellitus	22(15.8%)	140	30(19.5%)	153	0.001
Ferritin (mg/L)	604.1 [490.8-743.4]	90	427.3 [313.2- 539.1]	150	0.53
D-dimer(ng/L)	625.3 [542.9-720.2]	98	667.2 [585.3-749.1]	153	0.03
LDH (mg/L)	326.7 [306.7–348.01]	117	327.1 [286.7-373.1]	153	0.18
Procalcitonin(ng/L)	0.3 [0.2–0.6]	75	0.2 [0.2–0.3]	107	0.59
Lymphocytes	0.9 [0.8-1.0]	135	0.8 [0.7–0.9]	153	0.004
C-reactive protein(ng/L)	6.3 [5.4–7.3]	135	9.1 [7.9–10.5]	153	0.001
pCO_2	35.3 [31–38]	42	34 [32–38]	67	0.84
pO_2	73.6 [60.6–88.1]	42	71 [57–84]	67	0.87
FiO_2	24 [21–26]	119	24 [21–35]	152	0.48
Azithromycin	117 (83.6%)	140	141 (92.2%)	153	0.001
Lopinavir/ritonavir	126 (90%)	140	125 (81.7%)	153	0.001
Tocilizumab	66 (47.1%)	140	86 (56.2%)	153	0.55
Remdesivir	14 (10%)	140	11 (7.2%)	153	0.44
Anakinra	6 (4.3%)	140	36 (23.5%)	153	0.001
Hydroxychloroquine	0 (0%)		145 (94.8%)	153	
Corticosteroids:					
Methylprednisolone bolus	0 (0%)		77 (52%)	148	
Methylprednisolone	0 (0%)		90 (62.9%)	143	
Prednisone	0 (0%)		133 (86.9%)	153	
Mean total dose of corticosteroids (mg/day)			49.22 (56.16)	153	
Days with corticosteroid treatment			56.4 (32.2)	153	
Total corticosteroids dose/days			2131.6 (1196.3)	153	
Period from first symtoms to admission (days)	7 [4–9]	140	8 [5–12]	151	0.001
Hospitalization period (days)	9 [7–11]	140	19 [13–27]	150	0.001

Multivariable analyses showed that age (older than 50 years) (OR 4.85, 95% [CI 1.07–21.90], $p = 0.04$), having received a total dose of corticosteroids higher than 1600 mg (OR 6.00, 95% [CI 1.97–18.35], $p = 0.002$), and a total score on the initial chest CT scan more than 18 (OR 4.03, 95% [CI 1.27–12.76], $p = 0.02$) [8] were independently related to 1-year fibrotic-like changes.

Twelve months after discharge, 13 OP patients (14%) had FVC values lower than 80% of reference and 57 patients (63%) had a DLco lower than 80% of reference values (Table 3).

Discussion

Post-COVID-19 OP is the most common radiological pattern observed in COVID-19 infection, which in some cases can lead to fibrotic changes that cause respiratory failure. Similarly to our results, previous studies identify as a risk factor for developing OP-like pattern during the acute phase patient´s age, comorbidities such as chronic lung disease, and illness severity [13].

Specific laboratory abnormalities have also been associated with worse outcomes, including lymphopenia, elevated lactate dehydrogenase (LDH) and inflammatory markers (PCR, ferritin, and inflammatory cytokines [14].

Radiological follow-up presents a tendency to improve over time. However, patients with severe radiological involvement are more likely to develop fibrotic-like changes, which in our study appeared in 57% of patients with OP-like pattern in the acute phase. This high percentage could be due to the fact that our study was carried out during the first COVID-19 wave when there was no immunization by vaccines, in addition to including

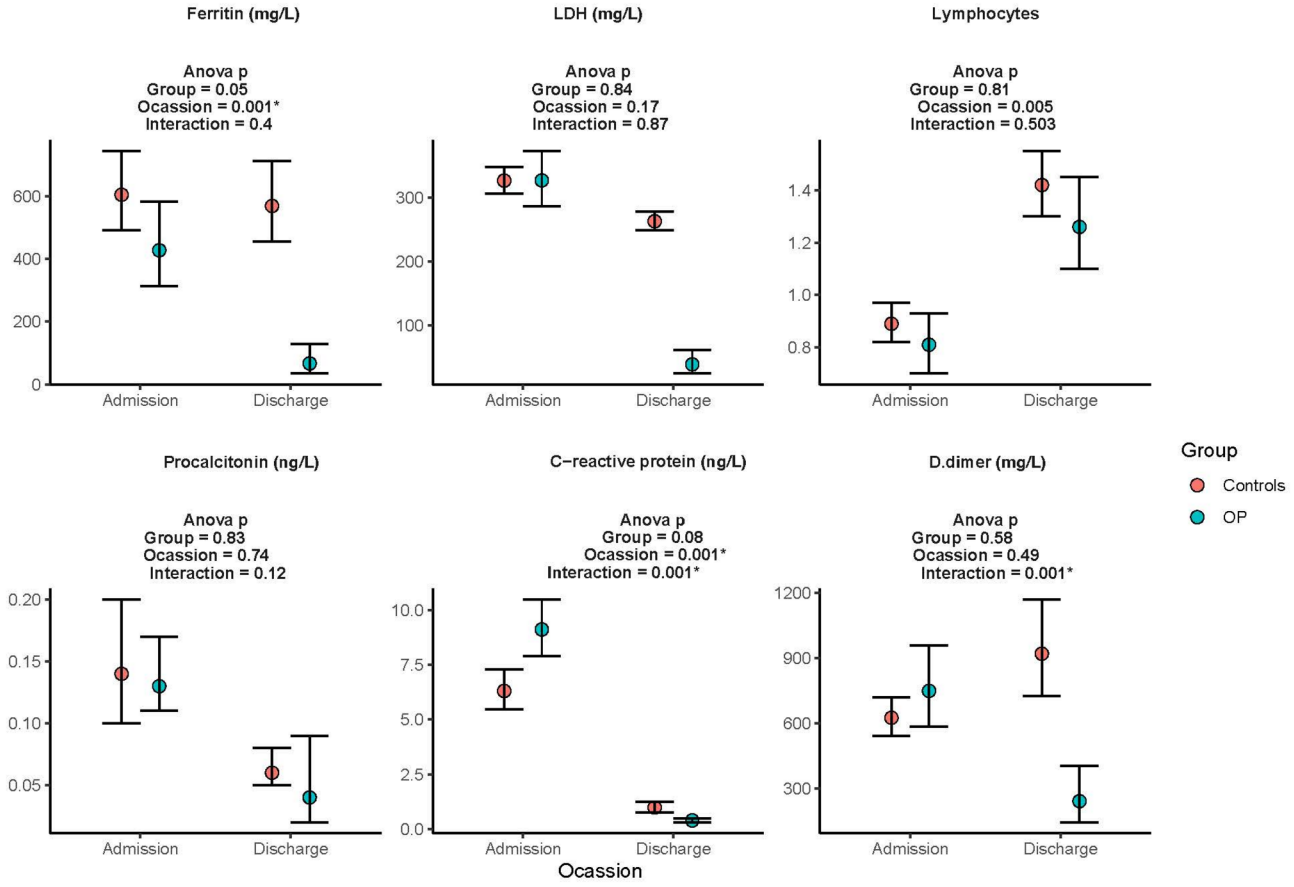

Fig. 1 Distribution (geometric mean and 95% confidence interval) of blood parameters according to period (admission/discharge) and persistent pneumonitis status at discharge (yes/no)

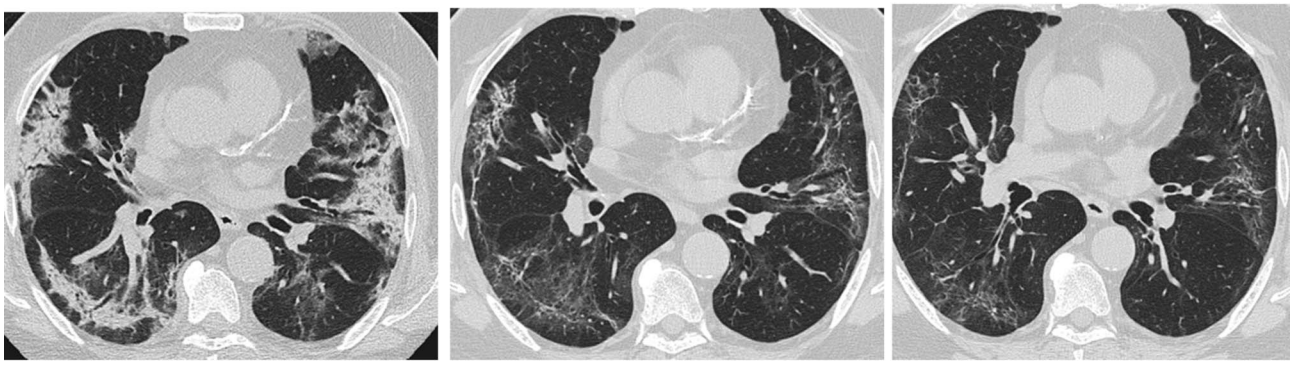

Fig. 2 Radiological evolution of OP-like pattern group during hospitalization, 1 month and 1 year after discharge

patients who were admitted to the ICU. Another important factor is the more aggressive nature of the virus variant's present during early phase of the pandemic compared to Omicron variant which primarily affects the bronchi instead of the alveoli [15].

Other studies also found fibrotic changes in the control radiologic images: Fabbri et al. [16] described at a median follow-up of three months fibrotic changes in 29% of patients defined as either reticulation, lung architectural distortion, interlobular septal thickening, traction bronchiectasis or honeycombing. Similar to our results, the UKILD post-COVID-19 study described as a risk factor of residual lung abnormalities male sex, age over 60 years of age, as well as severe acute illness percent predicted diffusing capacity for carbon monoxide (ppDLCO) less than 80%, in said study residual CT changes were seen in 65% of patients at three months, with 78% showing GGO, 34% showing septal thickening, and 33% showing reticular opacity [17].

Table 2 Radiological features at admission and during follow-up at one month and one year after hospital discharge

	OP diagnosis	1-month ($n=130$)	p-value*	1-year ($n=107$)	p-value**
Visual changes					0.013
Complete resolution		5(3.8%)		15 (14%)	
Subtotal resolution		41 (31.5%)		55 (51.4%)	
Partial resolution		75 (57.7%)		24 (22.4%)	
No changes		3 (4%)		12 (11.2%)	
Progression		6 (4.6%)		1 (1%)	
GGO	119 (97%)	116 (89%)	0.75	86 (80.3%)	< 0.001
Consolidation	118 (95%)	24 (19%)	< 0.001	1 (1%)	< 0.001
Bronchial dilatation	114 (93%)	65 (50%)	< 0.001	42 (39%)	0.06
Reticular pattern	106 (92%)	52 (40%)	< 0.001	50 (47%)	0.17
Fibrotic-like changes				61 (57%)	
PR				2 (2%)	
PB				11 (10%)	
TB				2 (2%)	
UIP				0 (0%)	
PR + PB				6 (0%)	
TB + PB				25 (23%)	
TB + PR				2 (2%)	
TB + PB + PR				13 (12%)	
CT score lung involvement	16.1 (4.3)	10.3 (5.1)	< 0.001	7.9+/-10.5	0.071
Right Upper L	2.5 (0.8)	1.7 (0.9)	< 0.001	1.2+/-1.0	< 0.001
Right Middle L	2.4 (0.9)	1.6 (0.9)	< 0.001	1.0+/-1.0	< 0.001
Right Lower L	3.2 (0.9)	2.0+/-1.0	< 0.001	1.53+/-1.13	< 0.001
Left Upper L	2.5 (0.9)	1.7+/-0.9	< 0.001	1.08+/-1	< 0.001
Lingula	2.5 (0.9)	1.6+/-1.0	< 0.001	0.97+/-0.94	< 0.001
Left Lower L	3.1 (0.9)	1.9+/-1.0	< 0.001	1.48+/-1.067	< 0.001

Abbreviations: *CT* computed tomography, *GGO* ground-glass opacity, *PB* parenchymal bands, *PR* pleural retraction, *TB* traction bronchiectasis, *UIP* Usual interstitial pneumonia

*Comparison between 1-month and OP diagnosis

**Comparison between 1-year and at OP diagnosis

Table 3 Results of pulmonary functional test at 3, 6 and 12 months since hospital discharge in OP group

	PFTs (3 months) $n=57$	PFTs (6 months) $n=53$	PFTs (1 year) $n=94$	p-value*
FEV_1(%)	92.3 (19.0)	90.8 (18.2)	96.1 (16.4)	0.09
FVC (%)	90.5 (16.6)	90.2 (15.1)	92.8 (14.1)	0.13
FVC < 80%	11 (19%)	15 (28%)	13 (14%)	> 0.99
FEV_1/FVC	90.8 (107.8)	74.9 (9.4)	77 (7.7)	0.30
DLCO (%)	75.3 (18.3)	74.0 (17.5)	75.4 (17.1)	0.37
DLCO < 80%	28 (52%)	33 (62%)	57 (63%)	0.37

*Comparison between 1-year and at 3-month

Han et al. [11] conducted a prospective study with COVID-19 patients requesting a follow-up thoracic CT scan six months after symptom onset. Fibrotic-like changes were observed in 35% of the patients, while the remaining 38% showed complete resolution and 27% residual ground-glass opacities or interstitial thickening. They also identified as risk factors for developing fibrotic changes age > 50 years and total CT score > 18 on the initial CT scan. In another study, Watanabe et al. [18] performed a meta-analysis of 15 studies; it is noteworthy that one year after COVID-19, 32.6% of patients presented residual abnormalities (ground-glass opacity 21.2% and fibrotic-like changes 20.6% were frequently observed), the frequency of CT abnormalities was higher in severe/critical cases than in moderate cases (37.7% vs. 20.7%).

Corticosteroids are the mainstay of treatment for organizing pneumonia [19]. When used acutely in managing acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2, corticosteroids have been associated with reduced mortality [20, 21]. However, corticosteroid use has known adverse effects such as delayed viral clearance, opportunistic infections, and suppression of the hypothalamic-pituitary-adrenal axis [22, 23]. In our study, a higher dose of corticosteroids (total dose of prednisone ≥ 1600 mg) was

independently associated with fibrotic changes in 1 year CT scan. However, this fact could also be due to a bias by indication since more severely ill patients are more prone to receive higher doses of treatment.

Overall, data from randomized trials support the role of glucocorticoids. In a meta-analysis [24] of seven trials included 1703 critically ill patients with COVID-19, glucocorticoids reduced 28-day mortality compared with standard care or placebo and were not associated with an increased risk of severe adverse events. In another meta-analysis of randomized trials [25] that evaluated interventions for COVID-19, glucocorticoids were the only intervention for which there was at least moderate certainty in mortality reduction or risk of mechanical ventilation compared with standard care. In another study, 837 patients were assessed four weeks after discharge, and 30 of them diagnosed with persistent interstitial lung changes received steroid treatment, resulting in significant symptomatic and radiological improvement [26]. In a study by Myall et al. involving 30 patients diagnosed with PCILD through a multidisciplinary team approach and displaying an organizing pneumonia pattern, the administration of prednisolone (at a dosage of 0.5 mg/kg) resulted in improvements in lung function, symptoms, and radiological appearances [27].

However, other studies, such as Sarkar et al. [28] found that in patients with COVID-19, corticosteroids may be associated with an approximately two-fold increase in mortality. Tlayjeh [29] et al. found no significant difference in mortality or mechanical ventilation required at the cost of prolonged viral clearance time. In the COLDSTER trial it was reported that high-dose prednisolone was not associated with any improvement in clinical, radiological, or quality-of-life outcomes when compared to lower-dose prednisolone [30].

These contradictory results may lead to doubts regarding the systematic use of corticosteroids as the standard treatment for SARS-CoV-2 OP. Additional studies are needed to determine the minimal dose of corticosteroids required to control inflammatory reactions without causing secondary effects.

Strengths and potential limitations

The study's strengths lie in its multicenter design, encompassing various hospitals representing diverse sociodemographic backgrounds. This approach ensures that the research captures a more comprehensive and representative sample of the population under investigation. Additionally, the study's meticulous characterization of participants adds further value by enhancing the quality and reliability of the data collected. This attention to detail in participant profiling helps to minimize potential confounding variables and increases the study's internal validity.

However, it is essential to acknowledge certain potential limitations in the study. One notable limitation is the relatively small sample size, which may affect the generalizability of the findings to a broader population. A larger sample size would provide a more robust basis for conclusions. Furthermore, the study's observational nature means it can establish variables' associations but cannot demonstrate causation. Therefore, caution should be exercised when interpreting causative relationships based solely on observational data. Also, in this study organizing pneumonia was not diagnosed on the basis of lung biopsies, only on radiological findings. Despite these limitations, the strengths of the multicenter design and careful participant characterization contribute significantly to the overall quality of the study.

Conclusions

Advanced age, previous respiratory diseases, and elevated C-reactive protein levels on admission are significant risk factors for the development of OP-like pattern in patients hospitalized due to COVID-19, and fibrotic-like changes may persist for a long time. Treatment with high doses of corticosteroids does not seem to provide advantages over lower doses in reducing radiological progression. This hypothesis should be tested in randomized prospective clinical trials using different corticosteroid doses.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41479-025-00169-9.

Supplementary Material 1.

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"Take home" message

Our study reveals that post-COVID-19 organizing pneumonia can lead to persistent fibrotic changes, regardless of corticosteroid dosage. We identified key risk factors and highlighted the need for further clinical trials.

Authors' contributions

JS contributed to the concept and design of the article, SC and JS drafted the article, all the remaining authors: SC, FG, MB, NA, AK, IC, SS, VT, AS, NS, MAN, AF, NP, JF, XA, AM, NR, SP, AV, ER, RF, AB, AS, JB, MM, OS, MS, AA and JG contributed to the acquisition of the data, revised the manuscript for intellectual content and approved the version to be published.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethical Review Board of the coordinating hospital (HCB/ 2020/0410) and all patients provided informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Servei d'Urgències, Hospital Clínic-Universitat de Barcelona, Barcelona, Spain
[2]Servei de Pneumologia, Institut Clinic Respiratori, Hospital Clínic, C/ Villarroel 170, Barcelona 08036, Spain
[3]Servei de Radiologia, Centre Diagnostic per la Imatge, Hospital Clínic-Universitat de Barcelona, Barcelona, Spain
[4]Servei de Pneumologia, Hospital San Joan de Deu, Sant Boi de Llobregat, Spain
[5]ISGlobal, Barcelona, Spain
[6]Servei de Medicina Interna, Hospital Clínic-Universitat de Barcelona, Barcelona, Spain
[7]Servei de Pneumologia, Hospital de Granollers, Barcelona, Spain
[8]Servei de Pneumologia, Hospital de Vic, Barcelona, Spain
[9]Servei d'Immunologia, Hospital Clínic-Universitat de Barcelona, Barcelona, Spain
[10]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[11]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBER), Barcelona, Spain
[12]Department of Biomedicine, Immunology Unit, University of Barcelona, Barcelona, Spain
[13]Servei de Malalties Infeccioses, Hospital Clínic-Universitat de Barcelona, Barcelona, Spain
[14]Servei de Pneumologia, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain
[15]Cátedra Salud Respiratoria, Universidad de Barcelona, Barcelona, Spain
[16]Facultat de Medicina, Universitat de Vic (UVIC), Vic, Spain

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