Factors Associated with Organizing Pneumonia after Respiratory Infection by SARS-CoV-2

Factores asociados a neumonía en la organización tras la infección respiratoria por SARS-CoV-2

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Abstract:

Introduction: Organizing pneumonia (OP) after SARS-CoV-2 is a sequel that impacts the recovery of patients; however, it is not clear which factors are associated with its development. Methods: Retrospective case-control study in adults with SARS-CoV-2 pneumonia for at least fourteen days, managed at the San Ignacio Hospital, Bogotá (Colombia). The clinical, paraclinical characteristics and outcomes were compared between patients who developed OP criteria (cases) and those who did not (controls). Factors associated with OP were evaluated. Results: 148 patients were included: 74 cases and 74 controls (age 57.8 ± 12.6 years; 62.2% men). The most frequent radiological pattern of OP was classic (70%). The controls had a more severe infection according to the News Score 2 > 6 points (67.6 vs. 52.7%; p = 0.002) and a higher mortality rate (13.5 vs. 4.1%; p = 0.04). After multivariate analysis, the only variable associated with OP was pneumonia with moderate severity by News Score (OR = 6.55; 95% CI: 1.76–24.4; p = 0.005). Conclusions: Moderate severity on admission is associated with OP. No other variable seems to be associated with its development. This might be explained by theories that propose that the pattern of lung injury in COVID-19 itself might be a spectrum of organizing pneumonia. New studies will be required to assess the impact of OP on these patients.
Keywords: pneumonia, SARS-CoV-2, coronavirus, organizing pneumonia.

Resumen:

Introducción: La neumonía en la organización (OP) tras el SARS-CoV-2 es una secuela que impacta la recuperación de los pacientes. No está claro cuáles factores se asocian con su desarrollo. Métodos: Estudio retrospectivo de casos y controles en adultos con neumonía por SARS-CoV-2 y síntomas por, al menos, 14 días, manejados en el Hospital San Ignacio (Bogotá, Colombia). Se compararon las características clínicas y desenlaces entre pacientes que desarrollaron criterios de OP (casos) contra los que no (controles). Se evaluaron los factores asociados a la OP. Resultados: Se incluyeron 148 pacientes, 74 casos y 74 controles (edad: 57,8 ± 12.6 años. Un 62,2 % de hombres). El patrón radiológico más frecuente de la OP fue el clásico (70%). Los controles se clasificaron en mayor proporción como severos, según la escala News (67,6% vs. 52,7%; p = 0,002), y presentaron una mayor tasa de mortalidad (13,5% vs. 4,1%: p = 0,04). La única variable asociada a la OP fue neumonía con severidad moderada por la escala News (OR = 6,55; IC95%: 1,76-24,4; p = 0,005). Conclusiones: La severidad moderada al ingreso se asocia con desarrollar OP. No hay otras variables que parezcan asociarse. Esto podría explicarse por las teorías que sugieren que el patrón de lesión pulmonar en COVID-19 sea en sí neumonía en organización. Se requerirán nuevos estudios para evaluar el impacto de la OP en estos pacientes.
Palabras clave: neumonía, SARS-CoV-2, coronavirus, neumonía en organización.

Introduction

The coronavirus infection pandemic that began in 2019 has generated more than 6.7 million deaths globally until January 2023 (1,2). In some patients with post-COVID-19 syndrome (3) and persistent symptoms, tomographic findings of progressive peripheral consolidations were noted, which led to the description of the first cases of organizing pneumonia after ARDS due to coronavirus (4).

A German registry reported that the frequency of post-COVID-19 organizing pneumonia was 12.5% (4), and it is currently recognized as a sequel that can appear approximately two weeks after infection (5). Previous studies suggest that it predominates in male, obese patients and in the sixth to seventh decade of life (6,7). Additionally, the observational study by Myall etal. (7) found that interstitial involvement after COVID-19 can appear with decreased biomarkers at the time of diagnosis, suggesting that the cause of interstitial lung involvement is not necessarily the same inflammation caused by the infection itself.

In these patients, biopsy is not always possible due to their hypoxemia and overall systemic compromise and in many cases steroid has been started using the clinical picture and tomographic pattern. Up to now, there is no evidence that makes it possible to identify the factors associated with the development of organizing pneumonia after coronavirus infection. Such information could help to anticipate the disease, and propose early treatment strategies, functional follow-up, and rehabilitation.

The objective of this study is to evaluate whether some demographic and clinical characteristics, such as age, sex, presence of obesity, lymphopenia, D-dimer, CRP (C-reactive protein), LDH (lactic dehydrogenase) elevations, and renal injury, are associated with the appearance of organizing pneumonia after respiratory infection by coronavirus, comparing the patients who developed this complication with those who did not.

Materials and methods

Observational case-control study. Patients included were over 18 years of age with SARS-CoV-2 viral pneumonia confirmed by molecular testing and persistent symptoms for at least fourteen days who were acutely managed and followed up at the San Ignacio University Hospital in Bogotá, Colombia, during the period of 2020–2021, and in which a chest CT scan taken at least 14 days after the onset of symptoms was available. We excluded pregnant patients, patients with coronavirus pneumonia who simultaneously had other diseases that were the indications for their hospitalization, and patients with a history of prior organizing pneumonia or an image of organizing pneumonia in the first chest CT scan taken before 14 days from the onset of symptoms, which would point to another cause that would explain said condition. The study was approved by the institutional research and ethics committee (MI-057-2021).

Information was collected regarding age, sex, presence of obesity, comorbidities, duration of symptoms, levels of D-dimer, lymphocytes, CRP, and LDH at admission, severity at admission, hospital mortality outcomes, and length of stay in the institution using a standardized format where this information was recorded systematically following an institutional protocol.

Cases were defined as those patients with persistent symptoms for more than fourteen days and tomography findings consistent with organizing pneumonia, which are:, ground-glass opacities, reticulation, and parenchymal consolidations. The radiologist evaluated both the corresponding pattern as well as the location of the lesions and their nature describing the pattern as: Consolidation or classic, crazy paving, nodular, perilobular, or fibrotic (8,9). Controls were defined as those with persistent symptoms after more than fourteen days and a chest tomography without such findings. The severity was defined with the News Score 2 scale for COVID-19 as: severe disease >6, moderate disease 5-6 and mild disease 0-4 points respectively (10). Renal injury was defined as an increase in creatinine >0.3 mg/dl, 1.5 times with respect to baseline or diuresis <0.5 ml/kg/h for 6 h (11) The cut-off points to define the levels of CRP, LDH, D-dimer, and lymphopenia as risk markers were defined a priori according to international recommendations (1).

Statistical analysis

Categorical variables were described as absolute and relative frequencies. Continuous variables were presented according to their distribution as mean and standard deviation, or median and interquartile range.

The Shappiro-Wilk test was used to test the assumption of normality. The comparison between cases and controls was made with a chi-square test, T test, or Mann-Whitney U test, depending on the type of variable.

In order to establish the factors associated with the appearance of organizing pneumonia, a logistic regression model was performed, initially univariate and subsequently multivariate, using the Stepwise Backward method. Variables with $p < 0.10$ in the univariate model were initially included in said model. Associated factors were those with an OR > 1, and protective factors were those with an OR < 1.

Lastly, Kaplan-Meier curves and the log rank test were performed to define whether there were differences in the survival functions of cases and controls. Stata software was used for statistical analysis (Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). and R 4.2.2 Project for statistical computing (R Foundation).

Results

148 patients, 74 cases, and 74 controls were included in the analysis. The average age was 57.8 ± 12.6 years (62.2% male). The most frequent comorbidities were arterial hypertension (35.8%), obesity (23.6%), and diabetes (17.6%). 60.1% of patients had severe pneumonia according to News Score 2, the average CRP was 12.6 mg/L, D-dimer 1547 ng/ml, lymphocytes 1055 cells/uL, and LDH 399 IU/L.

Among the cases of patients who developed organizing pneumonia, the most frequent pattern was the classic one (70%) and the less frequent one was fibrotic (1.3%) without obtaining cases of nodular pattern (Table 1).

TABLE 1.
Demographic, clinical and paraclinical variables of patients with viral pneumonia due to COVID who developed (cases) and who did not develop (controls) organizing pneumonia

Variable	Cases (n = 74)	Control (n = 74)	*p*-value
Age in years, mean (SD)	59.1 (13.21)	56.54 (12.00)	0.21
Male (n [%])	48 (64.8)	44 (59.5)	0.49
Smoking (n [%])	18 (25)	17 (22)	0.84
Obesity (n [%])	16 (21.6)	19 (25.7)	0.56
Arterial hypertension (n [%])	27 (36.5)	26 (3.15)	0.86
Diabetes mellitus (n [%])	14 (18.9)	12 (16.2)	0.66
Acute kidney injury (n [%])	4 (5.4)	0 (0)	0.043
Asthma (n [%])	1 (1.3)	2 (2.7)	0.56
COPD (n [%])	3 (4.0)	4 (5.4)	0.69
News Score 2 > 7 (n [%])	39 (52.7)	50 (67.6)	0.002
C reactive protein >10 mg/L (n [%])	43 (58.1)	50 (67.6)	0.23
D Dímer > 1000 ng/ml (n [%])	40 (54.1)	30 (40.5)	0.1
Lactate dehydrogenase > 350 mg UI/l (n [%])	38 (51.4)	42 (56.8)	0.51
Lymphopenia (< 1000 cm^3) (n [%])	47 (63.5)	41 (55.4)	0.32
Organizing pneumonia pattern (n [%])	Classic: 52 (70)		
	Crazy paving: 13 (17)		
	Perilobular: 8 (10.8)		
	Fibrotic: 1 (1.3)		
	Nodular: 0 (0)		
Length of stay (days), mean (IQR)	16 (6-27)	12 (8-19)	0.28
Steroid days, mean (IQR)	12 (5-18)	10 (7-10)	0.01
Intensive care admission (n [%])	34 (45.9)	39 (52.7)	0.41
Tracheal intubation (n [%])	30 (40.5)	29 (39.2)	0.867
Mortality (n [%])	3 (4.1)	10 (13.5)	0.04

SD: Standard Deviation; IQI: Interquartilic Range; IU: International Units; COPD: Chronic Obstructive Pulmonary Disease.

When comparing the baseline clinical variables between the cases and controls, it was found that both groups were similar without finding differences in pathological history or inflammation markers. However, the controls were classified as severe according to the NewsScore 2 in a greater proportion (67.6 vs 52.7%; $p = 0.002$) and presented a higher mortality rate (13.5 vs 4.1%; $p = 0.04$), while the cases developed more frequently kidney injury (5.4 vs 0%; $p = 0.043$) and received more days of steroids (median 12 vs 10 days; $p = 0.01$) (see Table 1).

In the univariate analysis, it was evidenced that the only variable related to presenting OP was pneumonia with medium severity by News Score 2, which was associated more frequently than pneumonia with low severity (OR = 6.55; 95% CI: 1.76–24.4; $p = 0.005$). High severity showed the same trend without achieving

statistical significance. In the multivariate analysis again, severity was the only variable that reached statistical significance for association with the development of organizing pneumonia (Table 2).

TABLE 2.
Variables analyzed for association with organizing pneumonia

Variable	Univariate analysis			Multivariate analysis		
	OR	CI 95 %	*p*	OR	CI 95 %	*p*
Male sex	1.25	(0.64–2.4)	0.5			
Age	1.02	(0.99–1.04)	0.21			
Obesity	1.24	(0.58–2.71)	0.56			
News Score						
Low	Reference	Reference		Reference	Reference	
Middle	6.55	(1.76–24.4)	0.005	6.55	(1.76–24.4)	0.005
High	2.15	(0.63–7.25)	0.22	2.15	(0.63–7.25)	0.22
C reactive protein >10 (mg/l)	0.66	(0.34–1.30)	0.235			
D Dimer >1000 (ng/ml)	1.72	(0.89–3.31)	0.1			
Lactate dehydrogenase >350 (IU/l)	0.8	0.42–1.54	0.51			
Lymphopenia	1.4	(0.72–2.70)	0.316			

OR: Odds ratio; IU: International units.

Finally, in the Kaplan-Meier analysis, it was found that presenting organizing pneumonia was associated with better survival compared to those who did not develop it (HR 7.25; 95% CI: 1.74–30.20; $p = 0.006$) (Figure 1).

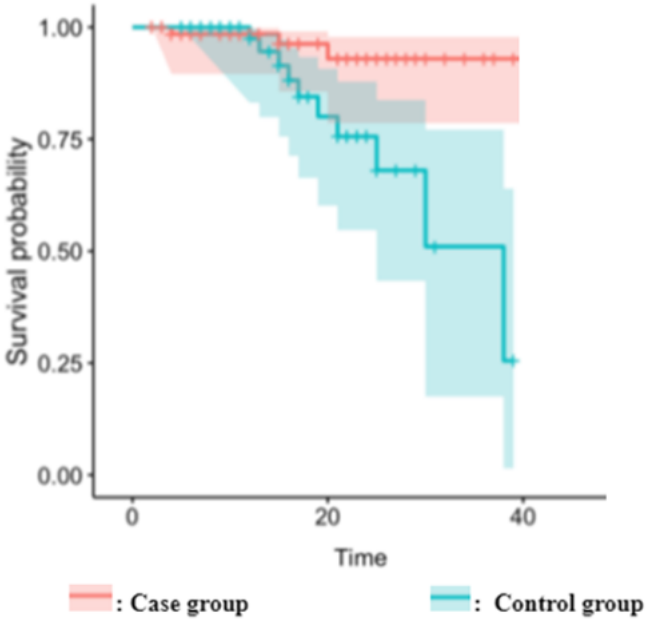

FIGURE 1.
Kaplan-Meier analysis illustrating the difference in hospitalization survival days between patients with organizing pneumonia following SARS-CoV-2 respiratory infection and those who did not develop it ($p = 0.006$)

Discussion

In the present study, we found that the baseline characteristics and inflammatory markers at the time of admission for viral pneumonia are similar between patients who develop and those who do not develop organizing pneumonia, and that the only factor associated with developing this complication is moderate clinical severity on admission.

Three mechanisms have been described that may favor the appearance of the characteristic lesions of interstitial lung disease that characterize organizing pneumonia: First, the development of diffuse alveolar damage, which consists of an alveolar and endothelial inflammatory process that favors exudate accumulation. The second mechanism is organizing pneumonia per se, where the infection favors lesions that cause leakage of coagulation proteins, together with fibrin, granulation tissue, and cell matrix, forming the characteristic connective tissue bodies. Finally, in the third phase, called fibrosing organizing pneumonia, fibrotic tissue is added that predominates in the histopathological study (12).

In our study, we found that a moderate clinical severity by News Score 2 is associated with the development of organizing pneumonia, even more significantly than a high severity. Additionally, we found no association with inflammatory markers. These findings contrast with those of Sinde et al., who found in a case-control study with 115 patients that the need for oxygen on day 21 (OR = 7.0; $p = 0.009$), C-reactive protein (OR = 1.1; $p = 0.028$), and a high severity of pneumonia (OR = 2.7; $p = 0.047$) implied a higher risk of organizing pneumonia (13). On the contrary, our findings are consistent with those reported by other authors (7), who report that the level of inflammation is similar between those who develop and those who do not develop organizing pneumonia, probably due to the proactive use of steroids without considering the exact moment of the natural history of the disease in each patient.

It is striking in our study that mortality was lower among those who presented with organizing pneumonia, which may be associated with the fact that the radiological findings are very similar to the typical patterns for

COVID-19 (12,14). Some authors suggest that the pattern of lung injury in COVID-19 may be precisely the development of organizing pneumonia, especially among patients who present with a high compliance phenotype such as that described by Gattinoni et al. (15). This could explain why the prognosis of patients with organizing pneumonia is not necessarily worse than that of those who do not develop it, since its detection leads to a more aggressive course of steroids and possibly greater immune modulation, as in our study, where the cases received steroids for a longer time. Prospective studies with a larger number of patients will be required to evaluate this hypothesis.

It will be important to evaluate in the future whether post-coronavirus pneumonia can impact health costs in relation to the drugs administered, hospital stay, and time required for supplemental oxygen, in addition to the costs of rehabilitation, pulmonary function tests and medical consultations that may be more frequent and in greater numbers than in a post-COVID-19 patient who has not had said complication.

The present study has limitations that must be recognized. The diagnosis of organizing pneumonia is normally supported by histopathological findings; however, an important limitation within the context of the pandemic is that the critical condition of the patients frequently prevented the performance of bronchoscopy and transbronchial biopsies (12), leading to the establishment of treatment with glucocorticoids only with clinical and radiological suspicion. This situation was common in our institution, as in many others where care for COVID-19 patients was provided, which is why we did not have histological confirmation of organizing pneumonia, therefore, a possible misclassification bias; however, this condition represents the reality of patient care in multiple institutions. Finally, another limitation is given by the retrospective nature of the case-control studies, which limits the evaluation of causality.

Conclusions

In the present study, we found that the baseline characteristics and inflammatory markers at the time of admission for viral pneumonia are similar between patients who develop and those who do not develop organizing pneumonia, and that the only factor associated with developing this complication is a moderate clinical severity on admission, presenting even higher mortality among patients who do not develop this complication. This is compatible with the proposed theories that organizing pneumonia might itself be part of the pathophysiological features of the disease. Further studies will be required to assess the long-term impact on patients.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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