

## ORIGINAL ARTICLE

# Influence of radiologic pattern and the presence of diffuse parenchymal lung disease on outcome in ventilated patients with COVID-19 pneumonia: impact on prognosis

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## Key words

organising pneumonia, COVID-19, mechanical ventilation, corticosteroids, intensive care unit.

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## Abstract

**Background:** Suspected organising pneumonia (OP) is a common finding in patients with severe coronavirus disease 2019 (COVID-19), but the impact on outcomes of the radiological patterns of diffuse parenchymal lung disease on outcome of these patients is still uncertain.

**Aims:** Investigate the presence of radiological images compatible with OP and its association with clinical outcomes in patients with COVID-19 submitted to invasive mechanical ventilation (IMV).

**Methods:** Retrospective, unicentric cohort study composed of patients who required IMV and underwent chest computerized tomography to investigate secondary complications of COVID-19. We compared patients with radiological findings characteristic of suspected OP with those without this condition. The main outcome was hospital mortality.

**Results:** Two hundred and ten patients were included, and 65 had signals compatible with OP. All patients with suspected OP were treated with corticosteroids. There was no difference in IVM-free days until day 28 between the groups (median, 0 days; interquartile range [IQR], 0–14.8) in the group with suspected OP vs 0 days (IQR, 0–11) in the group without suspected OP ( $P = 0.14$ ). In univariate analysis, the presence of suspected OP was associated with lower hospital mortality; however, after correction for potential confounding variables, it was not associated with the outcome, even after matching by propensity score in patients without this condition.

**Conclusion:** OP radiologic pattern in patients with severe COVID-19 is not associated with worse outcomes.

## Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), described for the first time in Wuhan, China, in December 2019, in a pneumonia outbreak.<sup>1</sup> COVID-19 may cause severe forms of respiratory failure. For instance, it is estimated that among

those patients hospitalised with COVID-19, up to 15% develop acute respiratory distress syndrome (ARDS).<sup>2</sup> COVID-19 pneumonia produces a computerised tomography (CT) pattern of diffuse parenchymal lung disease, characterised by bilateral, peripheral or multifocal, rounded ground-glass opacities, resembling organising pneumonia (OP). OP is characterised by the patchy filling of alveoli and bronchioles by granulation tissue and may occur as a pulmonary reaction to various injuries, including COVID-related ARDS.<sup>3</sup> OP is a diffuse parenchymal lung disease that is generally regarded as corticosteroid sensitive. While a short course of corticosteroids

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is the pharmacological mainstay of treatment for patients admitted to the intensive care unit (ICU) with COVID-19 pneumonia,<sup>4</sup> there is a paucity of data about the impact of COVID-related OP and its treatment on the prognosis of these patients. The main purpose of this study was to investigate the impact of suspected OP on prognosis in critically ill patients with COVID-19 submitted to invasive mechanical ventilation (IMV).

## Methods

We designed a retrospective cohort study that included patients admitted to the ICU at the Nossa Senhora da Conceição Hospital in Porto Alegre, Brazil, from June 2020 to April 2021. This study was approved according to national guidelines (Plataforma Brasil number 66240017.0.0000.5530).

## Patients

We screened patients admitted to the ICU with confirmed SARS-CoV-2 pneumonia undergoing IMV or non-IMV. We included patients who needed IMV and underwent chest CT to investigate secondary complications of COVID-19. The patients included were those who presented with a new deterioration of the clinical picture or even a lack of response to treatment, as interpreted by the assistant team, mainly related to a worsening of hypoxemia, pulmonary mechanics or a new clinical instability. The unfavourable clinical evolution could be attributable to a worsening of the clinical picture as well as to a lack of response to the implemented therapeutic measures. Patients who underwent chest CT for initial diagnostic or prognostic assessment, or in whom it was performed before the use of IMV, were excluded from the analysis. All patients were receiving prior corticosteroid therapy, mostly after the release of the results of the RECOVERY (Randomized Evaluation of Covid-19 Therapy) trial.<sup>4</sup> We divided the population of patients who received corticosteroids into two groups:

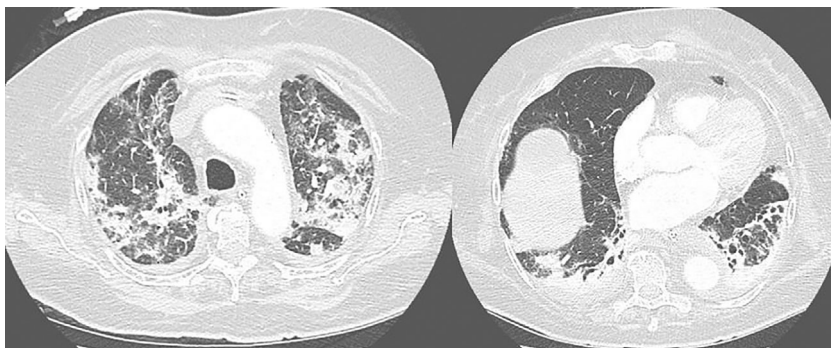
patients who received initial pulse therapy, defined as a loading dose  $\geq 500$  mg/day of methylprednisone for 3 days, and patients who received the standard dose of corticosteroids, defined as a dose  $\geq 1$  mg/kg/day of prednisone (or another corticosteroid with an equivalent dose). The corticosteroid regimen was at the discretion of the attending physician, as there are no accurate data in the literature suggesting the superiority of one corticosteroid regimen compared with another in this clinical setting. Patients did not receive antiviral drugs, anti-interleukin 6 or monoclonal antibodies in their COVID-19 treatment.

## Data collection

We reviewed the chest CT scans to assess findings suggestive of OP. The diagnosis of OP was made based on radiology findings by experienced radiologists in chest CT who were blinded to clinical outcomes. The radiologic findings characteristic of suspected OP include the presence of bilateral patchy consolidation areas with subpleural and/or peribronchial distribution; perilobular pattern with thick, ill-defined linear opacities with a polygonal or arcade appearance; and/or reverse halo sign (Figs. 1,2). We additionally collected the following clinical characteristics of the studied population: age, sex, duration of symptoms before the performance of CT scan, previous days on mechanical ventilation (MV), partial pressure of arterial oxygen to the fraction of inspired oxygen (P/F) ratio and sequential organ failure assessment (SOFA) score on the day of CT scan. In patients who underwent concomitant CT pulmonary angiography, we also assessed the association between the presence of pulmonary embolism and the outcomes.

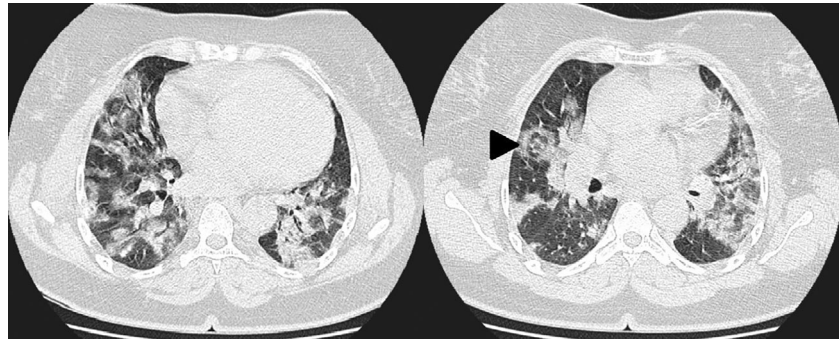
## Outcomes of interest

The primary outcome was in-hospital mortality. Secondary outcomes were the number of ventilation-free days, defined as the days that patients were both alive and free



**Figure 1** Radiologic features compatible with COVID-19-associated organising pneumonia. Computerized tomography (CT) axial scan showed bilateral consolidative and atelectatic changes in lesions in the lingula and lower lobes, with traction bronchiectasis. Areas of consolidation with peripheral predominance are seen in the upper lobes, with bronchiolectasis and septal thickening.

**Figure 2** Chest computerized tomography (CT) scan revealed bilateral, predominantly peripheral, opacities with ground-glass attenuation and consolidation. There are some perilobular consolidative opacities and inverted halo sign opacities (arrowhead).



of MV, and the incidence of secondary infections. We reported the incidence of bloodstream infections (BSIs), defined as the growth of a noncommensal organism on one or more blood cultures. To define a BSI caused by a common skin colonizer, such as coagulase-negative staphylococci, we required two or more blood cultures drawn from different sites and a clinical evaluation from one of our researchers. The diagnosis of lower respiratory tract infection (LRTI) was based on the presence of at least two of the following criteria: body temperature  $> 38^{\circ}\text{C}$  or  $< 36^{\circ}\text{C}$ , blood leukocyte count of  $> 10\,000$  cells/ $\text{mm}^3$  or  $< 5000$  cells/ $\text{mm}^3$ , purulent tracheal secretions and impairment of gas exchange. Urinary infection was defined as the growth of a bacterium in a culture urine sample from a patient with clinical symptoms. Peritonitis was defined as the growth of a pathogen from a surgical abdominal sample from a patient with abdominal symptoms.

### Statistical analysis

Descriptive statistics included frequencies and percentages for categorical variables and means, standard deviation, confidence intervals (CIs), medians and interquartile ranges (IQRs) for continuous variables. To

compare continuous variables, we used the Mann–Whitney  $U$  test. To analyse categorical variables, we used the chi-square test or Fisher exact test as appropriate. To assess the impact of OP on the outcomes, a backward polynomial logistic regression was performed with hospital mortality as the dependent variable and days on MV at diagnosis, P/F ratio, age, presence of OP and SOFA score at diagnosis as independent variables in the model. These variables were selected to enter in the model because of the presented  $P$  value of  $< 0.20$  in univariate analysis. We performed an additional analysis by propensity score matching by the nearest neighbour method. Statistical tests were two-tailed with significance defined as a  $P$  value  $< 0.05$ . We used R version 0.4.2 (R Project for Statistical Computing) for all analyses.

### Results

A total of 1005 patients had their electronic records reviewed. Overall hospital mortality in this population was 45%, with a mean Simplified Acute Physiology Score (SAPS) 3 score of 68 points and an admission SOFA score of 7.4 points. A total of 210 patients with IMV underwent a chest CT according to the study

**Table 1** Clinical and laboratory variables associated with hospital mortality

Variable	Unadjusted analysis (survivors vs nonsurvivors)		Adjusted analysis	
	OR (95% CI)	$P$ value	OR (95% CI)†	$P$ value
Organising pneumonia	0.51 (0.28–0.93)†	$< 0.001$	0.73 (0.34–1.57)	0.41
Days on MV	$10.7 \pm 8$ versus $7.5 \pm 6$	0.01	0.97 (0.93–1.02)	0.28
P/F ratio	$186 \pm 68$ versus $166 \pm 60$	0.02	1 (0.99–1)	0.05
Age	$52 \pm 12.9$ versus $63 \pm 11.8$	$< 0.001$	1.07 (1.04–1.1)	$< 0.01$
SOFA score	$5 \pm 5$ versus $7 \pm 7$	$< 0.001$	1.17 (1.05–1.32)	0.01
Male sex	1.3 (0.74–2.28)†	0.43		
Pulmonary embolism	0.8 (0.44–1.45)†	0.56		

CI, confidence interval; MV, mechanical ventilation; P/F, partial pressure of arterial oxygen to the fraction of inspired oxygen; SOFA, sequential organ failure assessment.

†Odds ratio (OR) for hospital mortality.

criteria. The median time on IMV before performing CT was 7 days (IQR, 2–9 days). The other clinical characteristics are shown in Table 1. A total of 65 (30%) patients had CT signs compatible with OP. All patients with suspected OP were effectively treated for this condition. Forty-eight patients received a standard dose of corticosteroids and 17 patients received a corticosteroid pulse therapy, with subsequent doses equivalent to 1 mg/kg/day of prednisone. The duration of treatment ranged from 8 days to 6 weeks. Patients who received corticosteroid pulse therapy had no lower in-hospital mortality compared with patients with suspected OP who did not receive pulse therapy (odds ratio [OR], 0.84 [95% CI 0.27–2.53];  $P = 0.756$ ). These patients were also not more likely to develop secondary infection compared with those who did not receive pulse therapy (OR, 2.07 [95% CI, 0.64–6.68];  $P = 0.219$ ).

Of the patients with suspected OP, 48 (73%) had secondary infection after starting treatment. Sixty-six (31% of the entire cohort) patients developed a BSI. Patients with suspected OP had a lower incidence of BSI when compared with those without this condition: 19.7% versus 37.4%, respectively (OR, 0.41 [95% CI, 0.21–0.81];  $P = 0.009$ ). A total of 113 patients developed an LRTI (53% of the entire cohort). Patients with suspected OP had an equivalent incidence of lower respiratory tract infection when compared with those without this condition: 52.1% versus 54.7%, respectively (OR, 0.9 [95% CI, 0.51–1.6];  $P = 0.724$ ). Microbiological data about BSI and LRTI are shown in Table S1. Seven patients developed other infections: five developed urinary tract infection and two developed peritonitis caused by *Candida* sp. Seventy-two (34%) patients in the total sample required tracheostomy for weaning from IVM. A total of 109 (52%) patients died in the ICU and 111 (53%) died during hospitalisation.

There was no statistically significant difference in age between patients who had suspected OP compared with those who did not have the diagnosis:  $56 \pm 13$  years versus  $61 \pm 13$  years ( $P = 0.06$ ). Patients with suspected OP had a lower P/F ratio compared with those who underwent CT but did not have this diagnosis:  $183 (\pm 70)$  versus  $158 (\pm 64)$  ( $P = 0.019$ ). These patients also had, on average, more days of symptoms ( $21 \pm 10.5$  days vs  $13 \pm 13$  days,  $P < 0.001$ ) and more days of IMV until the performance of CT ( $10.5 \pm 10$  days vs  $5 \pm 9$  days,  $P < 0.001$ ). There was no difference between groups regarding SOFA score on the CT day:  $6 (\pm 6)$  versus  $6 (\pm 6)$  ( $P = 0.22$ ).

There was no difference in IVM-free days until day 28 between the groups (median, 0 days [IQR, 0–14.8 days]) in the group with suspected OP versus 0 days (IQR, 0–11) in the group without suspected OP ( $P = 0.14$ ). In

univariate analysis, the presence of suspected OP was associated with lower hospital mortality; however, after correction for potential confounding variables, it was not associated with the outcome. The variables associated with in-hospital mortality were P/F ratio, age, and SOFA score at diagnosis (Table 1). After matching by propensity score between patients who developed and those who did not develop suspected OP, there was no difference in hospital mortality ( $P = 0.61$ ) or MV-free days ( $P = 0.11$ ) between groups.

Of the patients who underwent CT pulmonary angiography (187 patients), there was also no association between the presence of pulmonary embolism and in-hospital mortality. Patients diagnosed with pulmonary embolism ( $n = 67$ ) had no difference in IMV-free days on day 28 when compared with patients who did not have this diagnosis ( $n = 120$ ):  $8.2 \pm 10.6$  days versus  $5.1 \pm 8.4$  days ( $P = 0.055$ ).

## Discussion

In this study, we did not find an association between the presence of suspected OP, a complication commonly found in critically ill patients with COVID pneumonia, and in-hospital mortality when corrected for potential confounders. These results are in line with previous data in the literature, where the presence of radiological findings compatible with OP was associated with fewer ICU admissions and lower invasive MV requirement than patients with a non-OP pattern.<sup>5</sup> We analysed only critically ill patients submitted to invasive MV undergoing chest CT to investigate potential complications in their clinical course, as they had an unsatisfactory clinical response (new-onset fever, hypoxemia and ineffective weaning of MV) up to the time of the investigation. Even in this context of severity, the presence of radiological findings of suspected OP was not associated with worse outcomes in this population. Secondary OP is a complication present in several causes of lung injury, among which viral pneumonia stands out.<sup>6</sup> It may even be a chronic inflammatory response of the host to a persistent viral process, and the prognostic role of secondary OP in COVID remains inconclusive, as well as its difference in terms of clinical evolution in relation to OP secondary to other viral diseases. Our study has several limitations. There is an absence of histopathologic confirmation: all of the diagnoses of OP were based on imaging exclusively. All patients with suspected OP were treated for this, according to previous recommendations.<sup>6</sup> Therefore, there was no control group of patients with suspected OP without corticosteroid therapy, and since all patients received treatment, the impact of whether to treat OP on the prognosis of these patients cannot be

established. This specific subgroup of patients required a prolonged MV duration, and although the diagnosis of suspected OP was not associated with a longer time on MV due to a 'nonsignificant' *P* value, a clinically relevant impact cannot be ruled out. This limitation is also present in the diagnosis of pulmonary embolism, where a difference of 3 days, in this sample size, presented a 'nonsignificant' *P* value. Finally, different regimens of corticosteroid therapy were administered, lacking standardisation of treatment. Our cohort showed a high incidence of secondary infections throughout the course of the disease. This phenomenon is compatible with the severity of the underlying disease and the prolonged time on MV that these patients required. The use of different doses of corticosteroids was not associated with an increase in the incidence of secondary infections, similar

to previous data in the literature.<sup>7</sup> Many of these patients received antibiotic therapy concomitantly with the use of corticosteroids, and we cannot exclude this effect from the analysis of outcomes. We need new studies on this topic, especially an adequate clinical trial, to respond to this important question, considering the significant side effects of the use of prolonged corticosteroid therapy in critically ill patients, such as delirium, hyperglycaemia and weakness related to critical illness.

## Conclusion

The presence of a diffuse parenchymal lung disease compatible with OP is not associated with worse outcomes in severely-ill COVID-19 patients submitted to IMV.

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## Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

**Table S1.** Frequency of pathogens isolated from respiratory and bloodstream samples