


# Secondary organizing pneumonia after recovery of mild COVID-19 infection

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## Abstract

A 36-year-old male with diffuse large B-cell lymphoma on maintenance rituximab therapy presented to the emergency department with high fever and fatigue. A chest X-ray showed a lobar infiltrate, 40 days before admission the patient suffered from a mild coronavirus disease 2019 (COVID-19) infection and fully recovered. PCR nasopharyngeal swab was negative for COVID-19. Comprehensive biochemical, radiological, and pathological evaluation including 18-fluorodeoxyglucose positron emission tomography with computed tomography and transbronchial lung biopsy found no pathogen or lymphoma recurrence. Treatment for pneumonia with antibiotic and antifungal agents was nonbeneficial. A diagnosis of secondary organizing pneumonia (OP) was made after pneumonia migration and a rapid response to corticosteroids. OP secondary to a viral respiratory infection has been well described. Raising awareness for post-COVID-19 OP has therapeutic and prognostic importance because those patients benefit from steroid therapy. We believe the condition described here is underdiagnosed and undertreated by doctors worldwide. Because of the ongoing global pandemic we are now encountering a new kind of patient, patients that have recovered from COVID-19. We hope that this case may contribute to gaining more knowledge about this growing patient population.

## KEYWORDS

coronavirus, organizing pneumonia, post COVID-19, SARS coronavirus

## 1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is responsible for over 38 million cases and 634 157 deaths in the United States since January of 2020.<sup>1</sup> Accumulating evidence suggests that patients with hematological malignancies are more likely to develop severe disease.<sup>2</sup> Previous reports have suggested that immunocompromised patients may develop prolonged and persistent COVID-19 infection.<sup>3</sup> Secondary organizing pneumonia (OP), a form of diffuse interstitial lung

disease, is a unique condition associated with infections, systemic inflammatory diseases, medications, solid or hematologic malignancies.<sup>4,5</sup> This rare condition is often under-diagnosed even by experienced clinicians, a fact that has important clinical significance as many of these patients can benefit from corticosteroids treatment.<sup>6</sup> Secondary OP has been described as a consequence of severe COVID-19 in several reports,<sup>7,8</sup> and other authors have suggest that this condition may be underdiagnosed worldwide.<sup>9</sup> We present a case of secondary OP after recovery from mild COVID-19 infection in a 36-year-old male with diffuse large B-cell lymphoma on maintenance rituximab treatment.

## 2 | CASE PRESENTATION

A 36-year-old male with a history of diffuse large B-cell lymphoma 2 years prior, presented to the emergency department with 7 days of spiking fever, chills, fatigue, nausea, and abdominal discomfort.

He was married with two children, had a normal body index mass of 26, did not smoke, drank alcohol only socially, and did not use recreational drugs.

In 2018 follicular lymphoma with monoclonal plasma cell differentiation was diagnosed by excisional lymph node biopsy. 18-Fluorodeoxyglucose (FDG) positron emission tomography (PET) with computed tomography (CT) showed enlarged spleen with lymphadenopathy above and below the diaphragm. The lymphoma was classified as high risk and treated with RCHOP chemotherapy, after 6 cycles, a PET CT shows no evidence of 18F-FDG-avid disease. The patient was assigned to receive maintenance rituximab therapy for the following 2 years. The lymphoma was in remission according to regular hematologic follow-up, including timely PET-CT scans. He had no other comorbidities.

Forty days before admission, the patient suffered from mild COVID-19 infection. The patient suffered from fatigue and high fever, without shortness of breath or cough. A diagnosis of COVID-19 was confirmed by a positive PCR swab test. He was completely stable, with no need for oxygen support, he did not receive any treatment other than antipyretic medication. His symptoms lasted for 7 days, and no hospitalization was required. According to local health regulations, after resolution of symptoms and two negative PCR swab tests, the patient was considered recovered. However, a small amount of virus residual and pulmonary infiltration may have remained after recovery, especially in an immunocompromised host.<sup>3,10</sup>

On admission patient's temperature was 39.3°C, blood pressure, 101/57 mmHg; pulse, 88/min; respiratory rate, 16/min; and oxygen saturation, 99% on room air. On physical examination, the patient appeared weak, auscultation of the lungs revealed normal breath sounds, an enlarged spleen was palpated, the remainder of the physical examination was normal. Laboratory workup revealed elevated CRP (7.62 mg/dl) and slight lymphopenia (0.82  $10^3/\mu\text{l}$ ). White blood count, Creatinine, and blood gas were normal. PCR nasopharyngeal swab test for SARS-COV-2 was negative, urine dipstick was negative for leucocyte or nitrites. Chest X-ray demonstrated minimal opacity in the right upper lobe, blood and urine cultures were drawn. A day later, point of care ultrasound revealed right lung consolidation, a second lung X-ray demonstrated right upper lobe infiltrate, and treatment for community-acquired pneumonia with ceftriaxone was initiated. Nasal swab PCR for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, Adeno virus and other respiratory infections were negative as well as *Legionella pneumophila* urinary antigen test.

On Day 3 of admission, the patient continued with symptoms of fatigue, but no dyspnea was present, his fever was 38.9°C, doxycycline therapy was added for atypical pathogens coverage (e.g., *Coxiella burnetii*, *Mycoplasma pneumoniae*). Serological testing for Q fever, Brucella, *Rickettsia conori*, *Rickettsia typhi* and PCR tests for EBV and CMV were negative. Urine, sputum, aerobic and anaerobic

blood culture were taken daily and showed no growth. Sputum samples were negative for mycobacterium, a serum antigen enzyme-linked immunosorbent assay (ELISA) for galactomannan was negative, stool sample showed no evidence of bacterial or parasite PCR.

On Day 6 of admission, the patient continued with symptoms of fatigue and high fever without improvement, his oxygen saturation was 95% in ambient air. Chest, abdomen and pelvic CT scan was performed to search for focus of infection, it showed extensive right pulmonary infiltrates and enlarged spleen, empirical treatment with Piperacillin/Tazobactam and Voriconazole for fungal coverage was initiated. Treatment with Piperacillin/Tazobactam did not show any clinical response, and after 4 days the treatment was switched to Levofloxacin, however, the patient remained weak with high fever.

On Day 7, a bronchoscopy with a transbronchial lung biopsy was performed, the specimen was negative for Tuberculosis, *Nocardia*, *Legionella*, or other bacteria. ELISA for galactomannan was negative as well as other fungal infections. Pathologic tissue examinations revealed reactive bronchial epithelial cells, goblet cells, macrophages and mixed inflammatory cells. Atypical cells, fungi organisms or *Pneumocystis carinii* bacterial colonies were not seen, CMV immunostaining was negative.

*Candida albicans* was isolated from the bronchoalveolar lavage (B.A.L), no significance was attached to this finding because the patient was clinically stable. The bronchoalveolar-lavage (B.A.L) specimen was positive for COVID-19, SARS-CoV-2 RT-PCR cycle threshold (Ct) values were 26 for E gene and 28.2 for N gene.

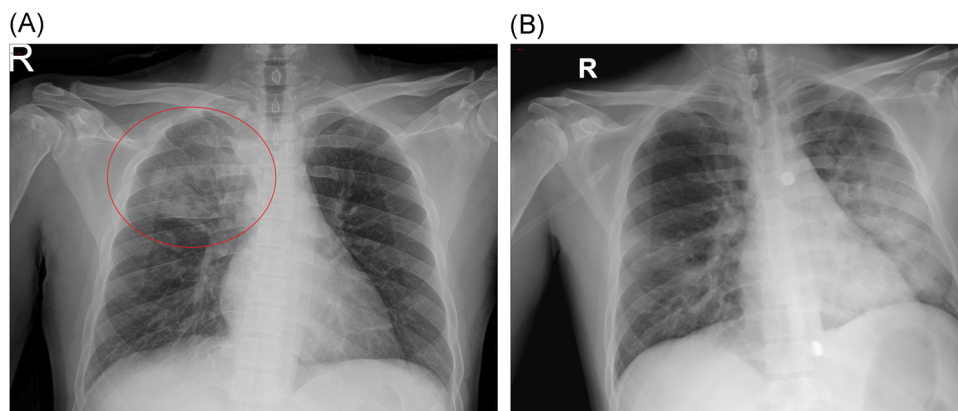
On Day 13 chest X-ray showed bilateral interstitial infiltrates with resolution of the right upper lobe opacity (Figure 1). Rheumatological autoantibody panel was negative. Working diagnosis at that point was COVID-19 syndrome, so antibiotic and antifungal treatment was stopped and treatment with corticosteroids was initiated, after two doses of corticosteroids his clinical condition improved, and the fever abated.

On Day 15 a whole body 18F-FDG PET/CT revealed extensive pulmonary infiltrates with increased uptake on the entire left lung and right lung base (Figure 2). A hypodense lesion in the spleen, likely associated with infarction was demonstrated, no mediastinal or other lymph node involvement was observed. Treatment with enoxaparin was added. Echocardiography showed preserved left ventricular systolic function and no evidence of vegetation.

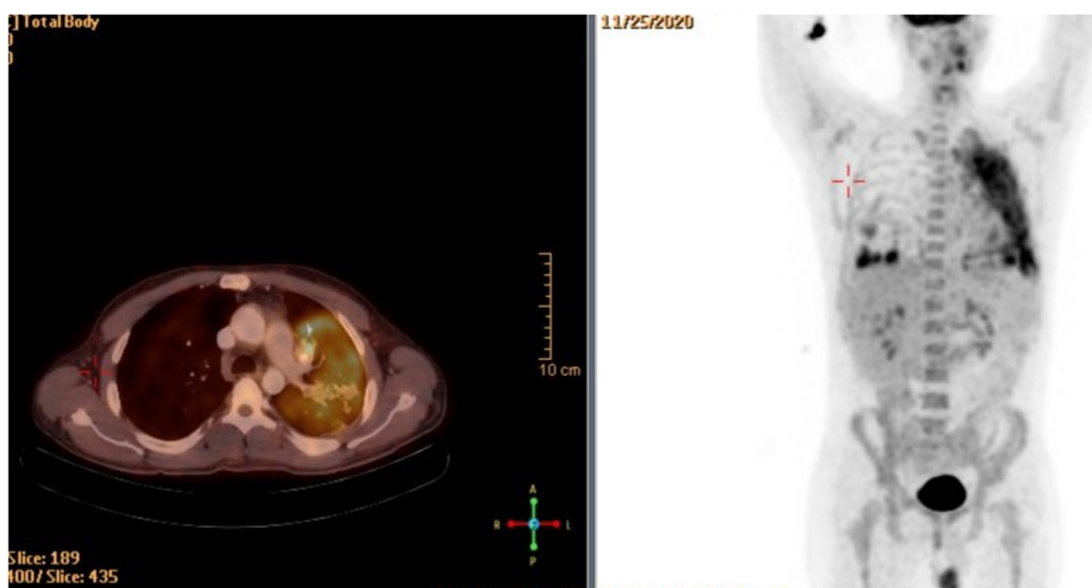
He was discharged on Day 20 in a good general condition after 8 days of corticosteroids and enoxaparin treatment. Timeline of clinical parameters, biomarkers and treatment are shown in Table 1. Currently, the patient is on anticoagulant therapy and a steroid taper, he went back to work and reports no functional decline.

## 3 | DISCUSSION

COVID-19 has a vast spectrum of clinical manifestations, from asymptomatic disease through different degrees of organ dysfunction to death. Immunocompetent patients usually recover after one to 4 weeks, while immunocompromised hosts have an increased risk



**FIGURE 1** Chest X-ray performed on the 2nd day of admission (A) and on the 13th day (B)



**FIGURE 2** 18-Fluorodeoxyglucose (FDG) positron emission tomography (PET) with computed tomography (CT) performed on the 15th day of admission showing extensive pulmonary infiltrates with increased uptake on the entire left lung and right lung base

of prolonged and complicated disease.<sup>3</sup> Clinical features of COVID-19 are well-described, but evidence about the COVID-19 convalescent phase is still evolving. We report the clinical, biomedical, and radiological findings of secondary OP after recovery from a mild COVID-19 in an immunocompromised patient.

Initially, the patient presented with a high fever and a right upper lobe infiltrate and treatment for community-acquired pneumonia was initiated. When the patient did not respond to therapy, we performed an evaluation for other sources of infection, less common and opportunistic. When the patient did not respond to extended-spectrum antibiotics with anti-fungal therapy our differential diagnosis was recurrence of lymphoma, infection, or lung disease. The whole body 18F-FDG PET/CT findings made the likelihood of lymphoma recurrence less likely, so was the possibility of bacterial or fungal infection due to negative laboratory tests and a lack of response to treatment.

PCR result of the nasopharyngeal swab for COVID-19 was negative, but the subsequent test of the bronchoalveolar lavage (B.A.L) specimen showed COVID-19 positive. B.A.L sample is obtained by bronchoscopy directly from lung tissue, therefore it is more sensitive to detecting small quantities of genetic material.<sup>11</sup> Positive B.A.L may indicate a small amount of virus residual that may remain for long periods after recovery, especially in an immunocompromised host on rituximab therapy.<sup>12,13</sup> According to the Centers for Disease Control and Prevention (CDC) guidelines continued shedding of the virus may occur as long as 143 days in an immunocompromised patient.<sup>10</sup> Other studies have shown that the virus is detectable in various human tissues for months. The finding of SARS-CoV-2 nucleic acid in tissues does not necessarily indicate clinical significance or infective potential.<sup>14</sup>

Lower Ct values indicate greater viral load with worse outcomes as suggested by some data.<sup>14</sup> In one study classified patients into

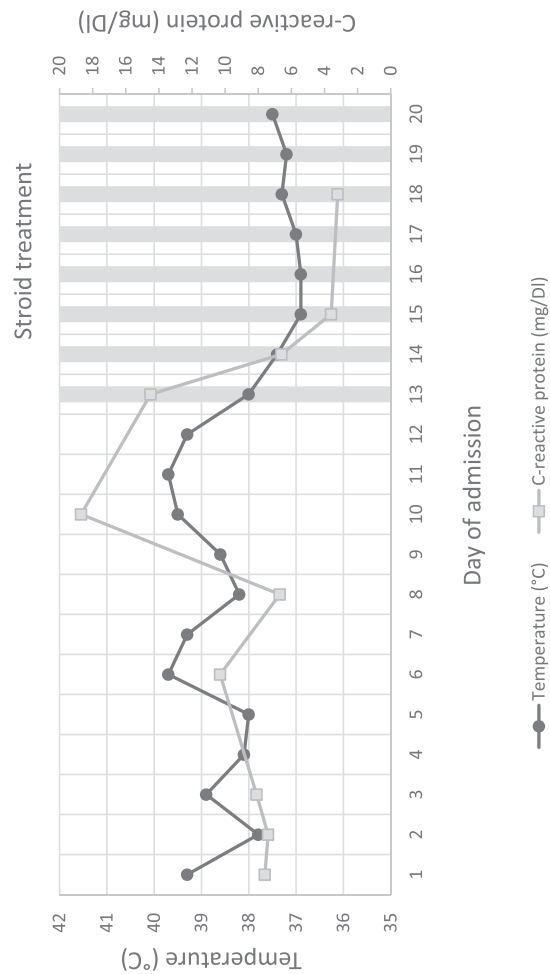
TABLE 1 Clinical parameters, blood biomarkers, and treatment

Day of admission	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
Maximal Body temperature (°C)	39.3	37.8	38.9	38.1	38	39.7	39.3	38.2	38.6	39.5
Average Blood pressure (mm/Hg)	101/57	102/70	99/54	105/68	93/60	112/71	99/58	99/55	102/59	99/59
Average Oxygen saturation (%)	99	94	98	98	95	94	97	98	99	95
White blood cell count (10 <sup>3</sup> /μl)	4.8	4.9	4.6	-	-	4.1	-	3.7	-	5.2
C-reactive protein (mg/Dl)	7.6	7.4	8.1	-	-	10.3	-	6.7	-	18.7
Treatment	Ceftriaxone	Ceftriaxone	Ceftriaxone + Doxycycline	Ceftriaxone + Doxycycline	Ceftriaxone + Doxycycline	Piperacillin-Tazobactam + Voriconazole	Piperacillin-Tazobactam + Voriconazole	Piperacillin-Tazobactam + Voriconazole	Piperacillin-Tazobactam + Voriconazole	Levofloxacin + Voriconazole
Day of admission	11th	12th	13th	14th	15th	16th	17th	18th	19th	20th
Maximal body temperature (°C)	39.7	39.3	38	37.4	36.9	36.9	37	37.3	37.2	37.5
Average blood pressure (mm/Hg)	104/57	99/55	100/59	102/55	107/58	99/56	110/60	102/56	101/60	102/56
Average Oxygen saturation (%)	95	94	96	95	94	95	98	99	95	98
	-	-	2.1	4.8	6.9	-	-	7.8	-	-

TABLE 1 (Continued)

Day of admission	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
White blood cell count (10 <sup>3</sup> /μl)	-	-	14.5	6.6	3.6	-	-	3.2	-	-
C-reactive protein (mg/Dl)	-	-	14.5	6.6	3.6	-	-	3.2	-	-
Treatment	Levofloxacin + Voriconazole	Levofloxacin + Voriconazole	Mythylprednisolone	Mythylprednisolone	Mythylprednisolone + Enoxaparin	Prednisone + Enoxaparin	Prednisone + Enoxaparin	Prednisone + Enoxaparin	Prednisone + Enoxaparin	Prednisone + Enoxaparin

Timeline of hospital admission, Temperature (°C), C-reactive protein (mg/Dl)



three groups: high Ct values ( $\geq 35$ ), intermediate Ct values (25–35), and low Ct values ( $\leq 25$ ). Follow up showed that the low-value group had a worse outcome.<sup>15</sup> This and most other studies calculate Ct values for nasal swab specimens when ours was from a B.A.L which is more sensitive and extracts more genetic material.<sup>11,15,16</sup> The SARS-CoV-2 RT-PCR Ct values were 26 for E gene and 28.2 for N gene, these values are not low, indicating that the positive test may be attributed to a small amount of virus residual without clinical significance. We believe that more evidence is needed to interpret the meaning of this finding.

Secondary OP or its idiopathic form, called cryptogenic organizing pneumonia, is type of a rare diffuse interstitial lung disease with alveolar proliferation of granulation tissue. OP is associated with drugs, infections, solid and hematological malignancies. The clinical presentation includes weakness, high fever, and dyspnea with an X-ray showing repetitive or migratory pulmonary opacities.<sup>4,5</sup> Antibiotic or antifungal treatment is ineffective and corticosteroid therapy is the first-line choice.<sup>6</sup> Op secondary to a viral respiratory infection has been well described over the years.<sup>5,17</sup> A first case of COVID-19 induced OP has been reported by Bae et. al followed by a report of 3 more cases.<sup>7,8</sup> Our case is unique because our young patient was not critically ill at any point and did not require any oxygenation therapy. The diagnosis is supported by a full evaluation that excluded other causes, migratory pneumonia, and rapid response to corticosteroids. Transbronchial lung biopsy had no specific findings, however, small lung biopsies are frequently inadequate for conclusive diagnosis. Thoracoscopic biopsies are usually required to obtain a sufficient sample of tissue.<sup>6,18</sup>

The scientific community is rapidly accumulating knowledge about the clinical, biochemical, and radiological features of COVID-19, however, data on COVID-19 recovered patients is still evolving. Some effects are already well described, among them are reduced pulmonary function, heart, and neurological injury.<sup>19,20</sup> However, we believe post-COVID-19 OP is underdiagnosed and undertreated by doctors worldwide. Because of the ongoing global pandemic it is crucial to recognize the complications or sequelae of COVID-19 patients after recovery. Raising awareness for post-COVID-19 OP has therapeutic and prognostic importance. When caring for COVID-19 recovered patients who suffer from pneumonia that does not respond to empirical antibiotic treatment this diagnosis should be considered. Steroid therapy is the first-line choice, it often results in rapid improvement in symptoms, radiographic and biochemical findings. Familiarity with this condition may spare invasive studies, hospitalization days and improve patient outcomes.

## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

**Evgeny Golbets and Alon Kaplan:** were responsible for drafting the manuscript. **Jenan Awesat and Yael Yagel:** extracted and interpreted the clinical, radiological and biochemical data. **Tali Shafat, Alan Jotkowitz, and Leonid Barski:** contemplated the main conceptual ideas. **Jenan**

**Awesat, Alon Kaplan, and Yael Yagel:** performed literature review. All authors revised the manuscript critically for intellectual content. All authors were part of a multidisciplinary team taking care of the patient. All authors approved the version to be published and participated sufficiently in the work to take public responsibility for the content.

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## REFERENCES

- Centers for Disease Control and Prevention. 2019 Novel coronavirus, Wuhan, China. Information for Healthcare Professionals. [https://covid.cdc.gov/covid-data-tracker/#cases\\_casesper100klast7days](https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days)
- Aries JA, Davies JK, Auer RL, et al. Clinical outcome of coronavirus disease 2019 in haemato-oncology patients. *Br J Haematol*. 2020; 190(2):e64–e67. <https://doi.org/10.1111/bjh.16852>
- Fung M, Babik JM. COVID-19 in immunocompromised hosts: what we know so far. *Clin Infect Dis*. 2021;72:340–350. <https://doi.org/10.1093/cid/ciaa863>
- Oymak FS, Demirbaş HM, Mavili E, et al. Bronchiolitis obliterans organizing pneumonia: clinical and roentgenological features in 26 cases. *Respiration*. 2005;72:254–262. <https://doi.org/10.1159/000085366>
- Drakopanagiotakis F, Paschalaki K, Abu-Hijleh M, et al. Cryptogenic and secondary organizing pneumonia: clinical presentation, radiographic findings, treatment response, and prognosis. *Chest*. 2011; 139:893–900. <https://doi.org/10.1378/chest.10-0883>
- Wells AU, Hirani N. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax*. 2008;63(Suppl 5), 1–58. <https://doi.org/10.1136/thx.2008.101691>
- Bae I-G, Hong K-W, Yang JW, et al 2020. Persistent pneumonic consolidations due to secondary organizing pneumonia in a patient recovering from COVID-19 pneumonia: A case report. doi:10.21203/rs.3.rs-37580/v1
- Vadász I, Husain-Syed F, Dorfmueller P, et al. Severe organising pneumonia following COVID-19. *Thorax*. 2021;76(2):201–204. <https://doi.org/10.1136/thoraxjnl-2020-216088>
- Kory P, Kanne JP. SARS-CoV-2 organising pneumonia: 'Has there been a widespread failure to identify and treat this prevalent condition in COVID-19?' *BMJ Open Respir Res*. 2020;7(1):e000724. <http://doi.org/10.1136/bmjresp-2020-000724>
- CDC Guidance for Discontinuation of Transmission-Based Precautions and Disposition of Patients with COVID-19 in Healthcare Settings (Interim Guidance). Available online: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html>.
- Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA—J Am Med Assoc*. 2020;23(18): 1843–1844. <https://doi.org/10.1001/jama.2020.3786>
- Walsh KA, Spillane S, Comber L, et al. The duration of infectiousness of individuals infected with SARS-CoV-2. *J Infect*. 2020;81:847–856. <https://doi.org/10.1016/j.jinf.2020.10.009>
- van Kampen JJA, van de Vijver DAMC, Fraaij PLA, et al. Shedding of infectious virus in hospitalized patients with coronavirus disease-2019 (COVID-19): Duration and key determinants. *Nat Commun*. 2021. 12(1):267. <https://doi.org/10.1038/s41467-020-20568-4>
- Zapor M. Persistent detection and infectious potential of sars-cov-2 virus in clinical specimens from covid-19 patients. *Nat Commun*. 2021;12:1384. <https://doi.org/10.1038/s41467-020-20568-4>
- Zacharioudakis IM, Prasad PJ, Zervou FN, et al. Association of SARS-CoV-2 genomic load with COVID-19 patient outcomes. *Ann Am Thorac Soc*. 2020;18:900–903. <https://doi.org/10.1513/annatsats.202008-931rl>

16. Rao SN, Manissero D, Steele VR, Pareja J. Correction to: a systematic review of the clinical utility of cycle threshold values in the context of COVID-19 (infectious diseases and therapy, (2020), 9, 3, (573-586), 10.1007/s40121-020-00324-3). *Infect Dis Ther.* 2020; 9(3):573-586. <https://doi.org/10.1007/s40121-020-00328-z>
17. Cornejo R, Llanos O, Fernández C, et al. Organizing pneumonia in patients with severe respiratory failure due to novel A (H1N1) influenza. *BMJ Case Rep.* 2010;2010:bcr0220102708. <https://doi.org/10.1136/bcr.02.2010.2708>
18. Bartter T, Irwin RS, Nash G, Balikian JP, Hollingsworth HH. Idiopathic bronchiolitis obliterans organizing pneumonia with peripheral infiltrates on chest roentgenogram. *Arch Intern Med.* 1989;149(2): 273-279. <https://doi.org/10.1001/archinte.1989.00390020023005>
19. Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5: 1265-1273. <https://doi.org/10.1001/jamacardio.2020.3557>
20. Huang Y, Tan C, Wu J, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res.* 2020; 21:163. <https://doi.org/10.1186/s12931-020-01429-6>

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