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# The impact of SARS-COV2 pandemic on the management oF IPF patients: Our narrative experience

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ABSTRACT

*Background:* The SARS-CoV-2 pandemic has changed the health-care systems around the world in a remarkable way. We describe the strategies adopted to cope with the limitations imposed by the pandemic to the access to health care by patients diagnosed with idiopathic Pulmonary Fibrosis (IPF).

*Material and methods:* We conducted a retrospective observational analysis including IPF patients under antifibrotic drugs (nintedanib and pirfenidone) that accessed to the Outpatient clinic of the University of Palermo, Italy. Patients received a phone number and an email address in case of any urgency and a virtual meeting was settled up monthly.

*Results:* 40 patients (M/F: 30/10) were followed up, 33 under nintedanib treatment, 7 under pirfenidone. Among patients under nintedanib, 1 patient reported high fever (T max 39 °C) and purulent sputum with no sign of infections, 1 had hemoptysis that was spontaneously resolved. 2 patients accessed to the emergency department for the worsening of dyspnea; 5 patients had diarrhea that resolved with symptomatic drugs in few days. 3 patients had an increase of alkaline phosphatase levels, leading to the withdrawal of the antifibrotic drug for 15 days, and subsequent normalization of the plasmatic levels. Among patients under pirfenidone, one subject had an increase of ferritin serum levels with no symptoms. The remaining subjects were in stable clinical conditions. None of the patients reported hospitalization or exacerbations, and did not experience antifibrotic withdrawal.

*Conclusions:* We were able to demonstrate that by implementing alternative ways to monitor the disease, patients did not incur in increased rates of acute exacerbations or higher frequency of side effects and antifibrotic treatment withdrawal.

## 1. Introduction

On 11 March 2020, the World Health Organization declared the Coronavirus disease 2019 (COVID-19) a pandemic [1]. COVID-19 disease, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an acute respiratory disease that can lead to respiratory failure and death [2]. In response to the pandemic, it was mandatory to increase measures and procedures focusing on personal hygiene, social distancing, patient isolation and public health quarantine. Accordingly, some concerns emerged on how to maintain access to the specialized integrated care medical centers for idiopathic pulmonary fibrosis (IPF) and guarantee regular follow-up visits and administration of antifibrotic drugs.

IPF is a progressive disease characterized by a poor prognosis with the median survival ranging from 2 to 5 year [3,4]. It is therefore of crucial importance to reassure that early diagnosis is pursued, and that treatment is initiated when indications are met with no delays, and regularly continued to attain the targeted objectives. Therefore, alternative pathways have been implemented or designed. As part of the medical response to disasters such as a world-wide pandemic, telemedicine has emerged as a potential solution to address this type of global challenge [5]. Telemedicine has the potential to improve access to health care resources and potentiate patient, limiting the risk of SARS-Cov-2 infection of fibrotic patients. It may include a variety of

*Abbreviations:* SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IPF, Idiopathic Pulmonary Fibrosis; ED, Emergency department; COVID-19, Coronavirus disease 2019; HRCT, High-resolution chest tomography; ARDS, adult respiratory distress syndrome.

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technologies to securely deliver remote health care such as live video-conferencing, audio-only visits as well as store technologies able to collect images and data [5]. In this context of outpatient clinics for lung fibrosis, these technologies offer the advantage of a timely diagnosis and the institution of proper treatment with reduced need for physical contact. Herein, we describe the strategies adopted to cope with the limitations imposed by the pandemic to the access to health care by patients diagnosed with IPF.

## 2. Material and Methods

Consecutive subjects attending the lung fibrosis outpatient clinic of the University Hospital of Palermo, Italy, with an ascertain diagnosis of IPF according to the most recent guidelines [6]' who were under regular treatment with antifibrotic drugs were offered, during the lockdown phase between March and May 2020, a phone dial number which was accessible 12h/die and an email address that was constantly monitored by medical personnel, in order to facilitate mutual sharing of documents such as laboratory exams or drug prescriptions. A virtual meeting with the patient was set up on monthly basis. A list of questions, specifically investigating the presence of fever, worsening of dyspnea or cough and symptoms related to drugs side effects, was administered telephonically to every patient. The compliance to antifibrotic drugs and rate of IPF exacerbations was recorded.

## 3. Results

Our experience refers to 40 patients (M/F: 30/10; under nintedanib: 33 patients; under pirfenidone: 7 patients) who were offered the follow-up programme, and were regularly contacted during this period. Among individuals under treatment with nintedanib, one subject experienced high fever (T max 39 °C) and cough with purulent sputum, which resulted negative for any microorganism. He was treated successfully with a short-term regimen of antibiotics. Another patient reported one single episode of hemoptysis that resolved spontaneously without treatment. Two patients had a worsening of their usual dyspnea resulting in a reduction of oxygen saturation, which required supplementary oxygen. Both patients were admitted to the emergency department (ED), where underwent clinical and radiological evaluations that excluded disease exacerbation. Five patients had diarrhea that resolved with symptomatic drugs in few days. Three patients had an increase of alkaline phosphatase levels, leading to the withdrawal of the antifibrotic drug for 15 days, and subsequent normalization of the plasmatic levels. The remaining subjects were in stable clinical conditions with high compliance to prescribed medication. Among patients on pirfenidone, one had an increase of ferritin serum levels in the absence of specific symptoms, and was sent for hematological consultation.

None of the above patients required hospitalization or antifibrotic treatment withdrawal. By reviewing the clinical charts from fibrotic patients followed during the previous year (March–May 2019), it resulted that patients followed during the pandemic did not show increased rates of acute exacerbations or higher frequency of side effects.

## 4. Discussion

The 2019 COVID-19 pandemic, characterized by severe acute respiratory syndrome [2], has affected virtually all aspects of care for patients with IPF with further implications for the maintenance and monitoring of therapy. IPF is a progressive disease in which lung function inexorably declines, leading to respiratory failure and eventually death. A large proportion of patients with IPF are treated with one of the two available antifibrotic drugs, pirfenidone and nintedanib, that have been shown to slow the rate of lung function decline [7,8]. The most devastating complication of IPF is acute exacerbation, which has an almost uniformly poor outcome having an in-hospital mortality rate of greater than 50% [9]. Acute exacerbation of IPF is defined by the onset of rapid deterioration (within days to a few weeks) in symptoms, lung function, and radiographic appearance (bilateral ground-glass opacities and consolidation superimposed on a reticular pattern on HRCT) in the absence of heart failure, pulmonary embolism, or pleural effusion [9–11]. In IPF, acute exacerbations are characterized by clinical, imaging, and histological characteristics of diffuse alveolar damage. There is biological and epidemiological support for the concept that acute exacerbations of IPF could be triggered by respiratory viral infections. Wootton and colleagues [12] found that a small proportion of patients with acute exacerbation of IPF had evidence of viral infection, including coronavirus infection. The majority of patients with COVID-19 (81%) present with mild symptoms (fever, cough, and dyspnea), while 14% have respiratory distress and hypoxemia, and 5% will develop respiratory failure [13].

In the midst of a global pandemic, the medical world has scrambled to find alternative ways of providing clinical care. In patients with chronic diseases like IPF, it may be appropriate to reduce the frequency of hospital visits during the COVID-19 pandemic to minimize patient contact with the health-care system, while still ensuring that patients receive appropriate medical care to maintain optimal adherence to treatment. In this exceptional scenario, telemedicine is increasingly available. Telemedicine can include a variety of technologies to securely deliver remote health care [14]. We were able to demonstrate that by implementing alternative ways to monitor the disease, patients did not incur in increased rates of exacerbations, indirectly confirming the utility of remote home monitoring. Larger studies, particularly randomized trials, are needed to confirm our observations.

## 5. Conclusions

We confirm the utility of home monitoring care system as a promising new support of the outpatient clinic routine. COVID-19 pandemic started to change the approach of how clinicians follow patients with severe chronic respiratory diseases. The introduction of telemedicine may be a useful tool to home-monitor stable patients under antifibrotic treatments.

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## Ethics approval

Not applicable.

## CRediT authorship contribution statement

**Alida Benfante:** Conceptualization, design, Methodology, Writing – original draft, Writing – review & editing. **Riccardo Messina:** Data curation, Methodology, review. **Ilaria Piccionello:** Resources, Visualization, Investigation, data collection. **Rosangela Di Liberti:** Resources, Visualization, Investigation, data collection. **Stefania Principe:** Data curation, Writing – review & editing. **Nicola Scichilone:** Writing – review & editingWriting-reviewing and editing, Conceptualization, design, Supervision.

## Declaration of competing interest

The authors confirm that there are no known conflicts of interest associated with this publication.

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## References


[1] World Health Organization. Coronavirus disease (COVID-19) outbreak (**Error! Hyperlink reference not valid.**).

[2] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

[3] American Thoracic Society, Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American thoracic society (ATS), and the European Respiratory Society (ERS), Am. J. Respir. Crit. Care Med. 161 (2000) 646–664, https://doi.org/10.1164/ajrccm.161.2.ats3-00.

[4] American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias, Am. J. Respir. Crit. Care Med. 165 (2002) 277–304, https://doi.org/10.1164/ajrccm.165.2.ats01.

[5] N. Lurie, B.G. Carr, The role of telehealth in the medical response to disasters, JAMA Intern Med 178 (6) (2018) 745–746, https://doi.org/10.1001/jamainternmed.2018.1314.

[6] G. Raghu, M. Remy-Jardin, J.L. Myers, L. Richeldi, C.J. Ryerson, D.J. Lederer, J. Behr, V. Cottin, S.K. Danoff, F. Morell, K.R. Flaherty, A. Wells, F.J. Martinez, A. Azuma, T.J. Bice, D. Bouros, K.K. Brown, H.R. Collard, A. Duggal, L. Galvin, Y. Inoue, R.G. Jenkins, T. Johkoh, E.A. Kazerooni, M. Kitaichi, S.L. Knight, G. Mansour, A.G. Nicholson, S.N.J. Pipavath, I. Buendía-Roldán, M. Selman, W. D. Travis, S. Walsh, K.C. Wilson, American thoracic society, European respiratory society, Japanese respiratory society, and Latin American thoracic society. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline, Am. J. Respir. Crit. Care Med. 198 (2018) e44–e68, https://doi.org/10.1164/rccm.201807-1255ST.

[7] T.E. King Jr., W.Z. Bradford, S. Castro-Bernardini, E.A. Fagan, I. Glaspole, M. K. Glassberg, E. Gorina, P.M. Hopkins, D. Kardatzke, L. Lancaster, D.J. Lederer, S. D. Nathan, C.A. Pereira, S.A. Sahn, R. Sussman, J.J. Swigris, P.W. Noble, ASCEND Study Group, A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis, N. Engl. J. Med. 370 (2014) 2083–2092, https://doi.org/10.1056/NEJMoa1402582.

[8] L. Richeldi, R.M. du Bois, G. Raghu, A. Azuma, K.K. Brown, U. Costabel, V. Cottin, K.R. Flaherty, D.M. Hansell, Y. Inoue, D.S. Kim, M. Kolb, A.G. Nicholson, P. W. Noble, M. Selman, H. Taniguchi, M. Brun, F. Le Maulf, M. Girard, S. Stowasser, R. Schlenker-Herceg, B. Disse, H.R. Collard, INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis, N. Engl. J. Med. 370 (2014) 2071–2082, https://doi.org/10.1056/NEJMoa1402584.

[9] H.R. Collard, C.J. Ryerson, T.J. Corte, G. enkins, Y. Kondoh, D.J. Lederer, J.S. Lee, T.M. Maher, A.U. Wells, K.M. Antoniou, J. Behr, K.K. Brown, V. Cottin, K. R. Flaherty, J. Fukuoka, D.M. Hansell, T. Johkoh, N. Kaminski, D.S. Kim, M. Kolb, D.A. Lynch, J.L. Myers, G. Raghu, L. Richeldi, H. Taniguchi, F.J. Martinez, Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report, Am. J. Respir. Crit. Care Med. 194 (2016) 265–275, https://doi.org/10.1164/rccm.201604-0801CI.

[10] H. Tomioka, T. Sakurai, K. Hashimoto, H. Iwasaki, Acute exacerbation of idiopathic pulmonary fibrosis: role of Chlamydophila pneumoniae infection, Respirology 12 (2007) 700–706, https://doi.org/10.1111/j.1440-1843.2007.01119.x.

[11] C.I.S. Silva, N.L. Muller, K. Fujimoto, S. Kato, K. Ichikado, H. Taniguchi, Y. Kondoh, T. Johkoh, A. Churg, Acute exacerbation of chronic interstitial pneumonia: high-resolution computed tomography and pathologic findings, J. Thorac. Imag. 22 (2007) 221–229, https://doi.org/10.1097/01.rti.0000213588.52343.13.

[12] S.C. Wootton, D.S. Kim, Y. Kondoh, E. Chen, J.S. Lee, J.W. Song, J.W. Huh, H. Taniguchi, C. Chiu, H. Boushey, L.H. Lancaster, P.J. Wolters, J. DeRisi, D. Ganem, H.R. Collard, Viral infection in acute exacerbation of idiopathic pulmonary fibrosis, Am. J. Respir. Crit. Care Med. 183 (2011) 1698–1702, https://doi.org/10.1164/rccm.201010-1752OC.

[13] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention, J. Am. Med. Assoc. 323 (13) (2020) 1239–1242, https://doi.org/10.1001/jama.2020.2648.

[14] H.K.Y. Almathami, K.T. Win, E. Vlahu-Gjorgievska, Barriers and facilitators that influence telemedicine-based real-time, online consultation at patients' homes: systematic literature review, J. Med. Internet Res. 22 (2) (2020), e16407, https://doi.org/10.2196/16407.