Early COVID-19 lockdown in Greece and idiopathic pulmonary fibrosis: a beneficial "impact" beyond any expectation

To the Editor:

Idiopathic pulmonary fibrosis (IPF) is an irreversibly progressive diffuse lung disease characterised by a usual interstitial pneumonia (UIP) pattern. IPF presents with an ominous prognosis with a median survival of around 5 years [1]. The development of an acute exacerbation, histologically diffuse alveolar damage (DAD) upon UIP, represents the most devastating of its complications and leads to death in the majority of patients admitted to the intensive care unit (ICU) [2–4]. Viral infections in the setting of an altered host lung microbiome are likely important triggers of acute exacerbations of IPF and subsequent acute respiratory distress syndrome (ARDS) [4, 5].

In December 2019, a novel coronavirus was detected as an aetiologic agent of severe acute respiratory syndrome (SARS), named SARS coronavirus 2 (SARS-CoV-2). With the potential for multiorgan involvement, the disease named coronavirus disease 2019 (COVID-19) is easily transmissible through respiratory routes [6]. Around 5% of patients develop critical manifestations necessitating ICU support, with a mortality rate of 40% to 60% [7]. The mechanisms through which SARS-CoV-2 causes lung damage are only partly known. It is postulated that the inhaled virus initially binds to nasal epithelial cells and starts propagating towards the lower respiratory tract, reaching the alveoli, where it infects preferentially alveolar type II cells [8]. Extensive viral replication leads to their apoptosis and cell death, triggering through several inflammatory cascades, DAD, clinically presenting as ARDS [9]. SARS-CoV-2, for its potential to induce pneumonia, represents a novel infectious agent that could trigger life-threatening acute exacerbations in patients with IPF [10].

We hypothesised that Greek IPF patients might have presented a spike increase in both hospitalisations and deaths during the first phase of the new viral epidemic. In this retrospective study we assessed the frequency, characteristics and outcome of COVID-19 in IPF patients followed-up in 11 specialised referral centres and two dedicated private practices in Greece. Patients included in the study fulfilled American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society criteria for definite/probable UIP/IPF (550 patients); excluded were patients with indeterminate or alternative ILD diagnosis (around 15% in each registry) [1]. COVID-19 diagnosis was based on the European Centre for Disease Prevention and Control "case definition for coronavirus disease 2019 criteria" [11]. The study period ranged from 26 February, 2020 when the first COVID-19 case was confirmed in Greece to May 2020, where after a strict lockdown, authorities started to lift restrictions. During this time-period, 2632 COVID-19 cases and 146 deaths were officially reported distributed in every administrative region of the country [12]. IPF referral centres were located in university and tertiary hospitals across Greece. Patient management was accomplished mainly by telephone or/and video appointments and by electronic prescription of treatment. Hospitalisation was not utilised unless absolutely necessary. All registered IPF patients were contacted for informed consent. Demographic, epidemiological, functional, clinical and microbiology data were retrospectively obtained through medical records and/or hospital databases. Apart from COVID-19, any other lower respiratory tract infection necessitating hospitalisation, as well as disease outcome, was reported. Data concerning hospital admissions, lower respiratory tract infections necessitating hospitalisations and in-hospital deaths were compared with data of the same time-period of the year 2019. Patients deceased between May 2019 and

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During the lockdown, IPF patients experienced lower than expected COVID-19, suggesting that simple measures for the winter months, such as face masking, clean hands, physical distancing could be adopted as promising advances in non-pharmacological therapy https://bit.ly/2ISi2EV

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March 2020 were not included in the cohort examined in 2020. Data were analysed using SPSS 18.0 for Windows (SPSS Inc, Chicago, IL, USA). The study was approved by the medical ethics committee of the General University Hospital "Attikon", Athens, Greece (EBΔ 271/26-5-2020).

Overall, 550 patients, median (interquartile range (IQR)) age 74 (68–78) years, 80.7% male, 72% ever-smokers with a median (IQR) forced vital capacity 78% (64–91%) and DLCO 46% (34–59%) of predicted, respectively, and disease duration of 26 (12–43) months were included in the study. Receiving antifibrotic treatment were 458 (83.3%), 76 (13.8%) were under no treatment and 16 (3%) were receiving immunosuppressive treatment. The majority suffered from at least one comorbidity, such as arterial hypertension (51.3%), coronary artery disease (25.8%), diabetes mellitus (18.4%) and neoplastic disease (9.1%). Only 6.1% necessitated long-term oxygen therapy. Almost all patients were immunised against influenza (96.4%) and *Streptococcus pneumoniae* (87.1%). Only two patients (0.4%), one 60-year-old male

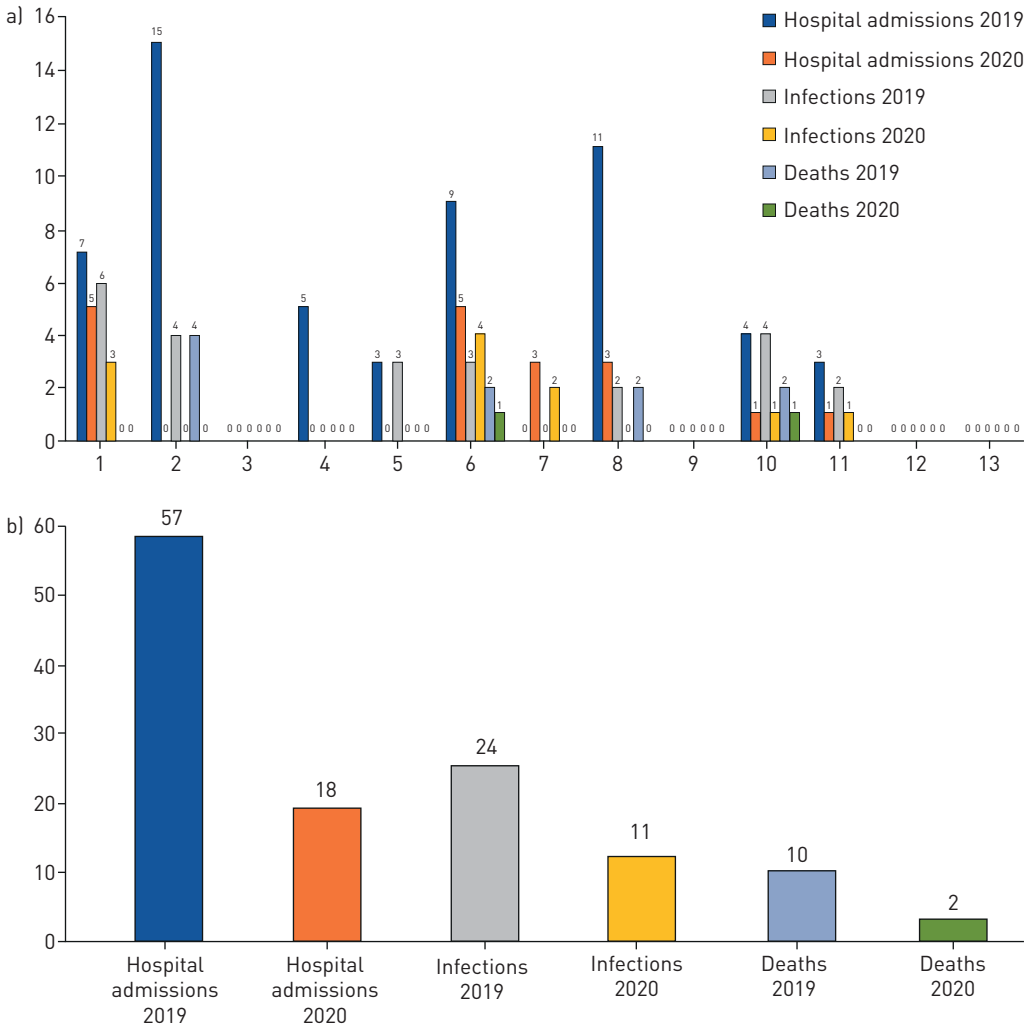

FIGURE 1 a) Histogram representation of the hospital admissions, lower respiratory tract infections necessitating hospitalisation and deaths in absolute numbers during two comparative 3-month time-periods (March to May 2019 and the lockdown period March to May 2020), regarding 550 idiopathic pulmonary fibrosis (IPF) patients followed-up in 11 specialist referral centres and two dedicated private practices in Greece. Numbers on the *x*-axis corresponds to each centre as follows: 1) "Attikon", Athens (39 patients); 2) "Iatriko" and "Sotiria", Athens (100 patients); 3) "G Papanikolaou" I, Thessaloniki (107 patients); 4) "Sotiria", Athens (33 patients); 5) Patras (74 patients); 6) "G. Papanikolaou" II, Thessaloniki (65 patients); 7) Larissa (52 patients); 8) Alexandroupolis (22 patients); 9) Heraklion (18 patients); 10) Ioannina I (16 patients); 11) Corfu (16 patients); 12) Messini (five patients); and 13) Ioannina II (three patients). b) Histogram representation of the overall hospital admissions, lower respiratory tract infections necessitating hospitalisation and deaths in absolute numbers during two comparative 3-month time-periods (March to May 2019 and the lockdown period March to May 2020) regarding 550 IPF patients followed-up in 11 specialist referral centres and two dedicated private practices in Greece.

and one 91-year-old female, first-degree relatives with recently diagnosed familial IPF, developed COVID-19 and survived. Finally, during the lockdown compared to the same time-period in 2019, a decreased median number (IQR) of hospital admissions (0 (0–3) *versus* 3 (0–8)), lower respiratory tract infections necessitating hospitalisations (0 (0–1.5) *versus* 2 (0–3.5)) and in-hospital deaths (0 (0–0) *versus* 0 (0–2)) were reported. Despite numerical decrease in all aforementioned outcomes, statistical significance was not reached, probably due to the small number of events (p=0.153, p=0.287 and p=0.390, respectively) (figure 1). All in-hospital deaths, 10 in 2019 and two in 2020 (COVID-19 negative) were related to acute IPF exacerbation.

This study shows that during the strict COVID-19 lockdown applied in Greece, patients with IPF experienced much lower than expected COVID-19. At the same time, besides discrepancies between centres that could be attributed mainly to the random development of events, the heterogeneity in the population of each region and the policies for in-hospital management of IPF, an overall decrease in both hospitalisations related to other lower respiratory tract infections and deaths were reported.

Given the high virulence of the novel virus and the already described vulnerability of the study population, this observation could be attributed to the beneficial impact beyond any expectation of early lockdown measures imposed all over the country. IPF patients proved to be a disciplined population, that by respecting scrupulously prophylactic measures when in close contact with treating physicians, effectively avoided several viral infections, including that of SARS-CoV-2. The results of the present study are in accordance with similar ones referring to other chronic lung diseases, such as COPD, demonstrating a significant decrease in the number of admissions for exacerbations in first 3 months of 2020, due to the adoption of protective measures [13]. One could hypothesise that other parameters could also play a role. However, for the moment no evidence exists that antifibrotic treatment may lower the risk of COVID-19 [14] and/or that intrinsic mechanisms could favourably alter the characteristics of COVID-19 in IPF. On the contrary, both COVID-19 and pulmonary fibrosis are considered severe diseases characterised by lung injury and dysregulated repair [14] and comorbid ILD is a risk factor for poor outcomes from COVID-19 [10].

Among the limitations of the study are its retrospective design and the potential bias related to missing patients. However, in this multicentre study it is very unlikely that IPF patients were hospitalised or deceased without being captured, since all hospitals of the IPF referral centres have also been designated COVID-19 referral centres.

Given the life-saving impact of the lockdown in IPF patients concerning both COVID-19 and other viral lower respiratory tract infections, one wonders whether limited and periodically applied lockdown measures should be inflicted each year during the winter months in this specific population. Based on the fact that the COVID-19 pandemic threatens both public health and human rights, we modern scientists could not impose such restrictive measures [15]. However, simple measures for the winter months, such as face masking, clean hands and physical distancing could be adopted and endorsed as the most recent and promising advances in non-pharmacological treatment in IPF.

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