Short Report

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Prevalence and outcomes of SARS-CoV-2 infection in ILD: Post-pandemic study in South Italy

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ABSTRACT

This retrospective study assessed the impact of SARS-CoV-2 infection on patients with interstitial lung disease (ILD) at two tertiary centers in Southern Italy between January 2022 and December 2023. The cohort included 282 ILD patients (mean age 69.6 years; 54.9% male), with common diagnoses such as idiopathic pulmonary fibrosis (33.3%) and connective tissue disease-associated ILD (18.7%). SARS-CoV-2 infection occurred in 130 patients (46%), mostly with mild or asymptomatic cases. Pneumonia developed in 18 cases, with 72.2% requiring hospitalization and 5 COVID-19-related deaths. Patients with pneumonia had higher rates of ILD progression (27.7%) and incidental post-infection ILD diagnoses (22.2%) than those with mild infection. Vaccination rates were high, correlating with favorable outcomes in most cases. Importantly, pneumonia cases were often associated with incomplete vaccination or complex comorbidities. Differentiating COVID-19-related lung changes from ILD progression proved challenging, highlighting the importance of specialized radiologic assessment. Excluding COVID-related deaths, mortality rates were similar regardless of infection status, suggesting a degree of resilience among ILD patients. The study concludes that with high vaccine coverage and careful follow-up, most ILD patients had stable outcomes after SARS-CoV-2 infection. However, pneumonia remains a risk factor for adverse outcomes, underscoring the need for long-term, specialized ILD care.

Key words: SARS-CoV-2, Interstitial Lung Disease, Pulmonary Fibrosis

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Since the global spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), its strong association with the lungs has continued to draw significant attention from the medical and scientific communities [1]. The emergence of viral variants and the widespread availability of vaccines have notably changed the clinical presentation of Coronavirus Disease 2019 (COVID-19) over time [2]. Despite this evolution, key questions about the virus-lung relationship remain unanswered. Two major concerns demand clearer, evidence-based insights. During the early waves of the pandemic, the lungs were the primary target of the virus, frequently causing severe pneumonia with high mortality, especially in the absence of effective treatments. The interstitial pattern often seen

in COVID-19 pneumonia raised fears of potentially irreversible fibrotic changes on chest CT scans in survivors. However, existing evidence remains mixed and inconclusive, requiring cautious interpretation and further research [3,4]. A second major concern is the potential impact of SARS-CoV-2 infection on the natural history of pre-existing interstitial lung disease (ILD). This worry is supported by data from other viral infections known to trigger the onset, worsening, or acute exacerbation of ILDs [5]. During the height of the pandemic, strict public health measures and widespread caution offered some protection for those with chronic illnesses, including ILDs [6]. Although these patients were recognized as vulnerable, no alarming trends emerged specifically for this group. Still, the ability to collect clinical data and conduct large-scale studies was severely hampered by the strain on healthcare systems [7].

In light of these considerations and taking advantage of the return to regular outpatient activities after the emergency phase, we aimed to assess the prevalence and clinical outcomes of SARS-CoV-2 infection in ILD patients followed at two tertiary centers in Southern Italy from January 2022 to December 2023. At each visit, structured data were collected on SARS-CoV-2 infection (diagnosis date, clinical course, hospitalization) and ILD status (clinical stability, progression, or death). SARS-CoV-2 infection was primarily patient reported. For cases of pneumonia requiring admission to our department, infection was additionally documented by a positive nasopharyngeal swab. All patients had at least one year of clinical and radiological follow-up to assess resolution of pneumonia-related changes and evaluate ILD progression, as defined by international consensus criteria [8]. For patients who died during hospitalization, data were obtained from hospital records via family members. Vaccination status (number of doses) was recorded. Patients with suspected vaccine related ILD progression were excluded. Data were retrospectively entered into an anonymized database, updated as of December 20, 2024. The study complied with the amended Declaration of Helsinki and received Ethics Committee approval (protocol AOC/0008746/2024). Informed consent was obtained from all participants or their next of kin. The study included 282 adults with ILD. Mean age was 69.6 ± 11.1 years, with 54.9% male. Former smokers made up 66.3% (n = 187), with a mean smoking history of 31.8 ± 27 pack/years. Average body mass index (BMI) was 27.5 ± 4.6 kg/m^2. Most patients (85.8%) had at least one comorbidity, most commonly hypertension (51.2%) and type II diabetes (20.6%), followed by gastro-esophageal reflux disease (28%), ischemic heart disease (15.2%), and sleep apnea (20.6%). A total of 101 patients (35.8%) were on antifibrotic therapy: nintedanib (65.3%) or pirfenidone (34.6%). The most frequent ILD diagnoses were idiopathic pulmonary fibrosis (IPF, 33.3%) and connective tissue disease-related ILD (CTD-ILD, 18.7%), followed by smoking-related ILD (11.3%), chronic hypersensitivity pneumonitis (cHP, 9.9%), sarcoidosis (6.7%), and other ILDs (20.2%). During the study, 106 patients (37.5%) received a new ILD diagnosis. Of our overall study population, a significant prevalence of SARS-CoV-2 was observed, with a total of 130 patients (46%) reporting infection. Notably, most of these cases were asymptomatic or mild. Mild infection was clinically defined as a self-limiting form of the disease, characterized by few symptoms, the absence of pneumonia and no requirement for hospitalization or supplemental oxygen therapy. Pneumonia developed in 18 patients, with 13 (72.2%) requiring hospitalization. No major differences in age, sex, BMI, or smoking history were noted between mild and pneumonia cases. However, hypertension and ischemic heart disease were more common in the mild group (74.7% vs. 44.4% and 20% vs. 0%). Type II diabetes was similarly distributed. In the mild group, 33% had IPF and 20.7% had CTD-ILD. Pneumonia cases mostly involved IPF (44.4%) and cHP (33.3%). Antifibrotic therapy was evenly distributed. Vaccination coverage was high: 98.5% in the mild group and 88.8% in the pneumonia group, with an average of 2.8 doses. Most (89.2%) with mild infection had at least two vaccine doses; two pneumonia patients (11%) were unvaccinated. Three clinical outcomes were identified post-infection (Figure 1). 1) Among the 114 patients with stable disease, 5 (4.4%) presented with pneumonia, while 109 (95.6%) experienced mild infection. 2) For the 12 patients with disease progression, 5 (41.7%) developed pneumonia and 7 (58.3%) had mild infection. 3) Among the 6 patients with incidental ILD

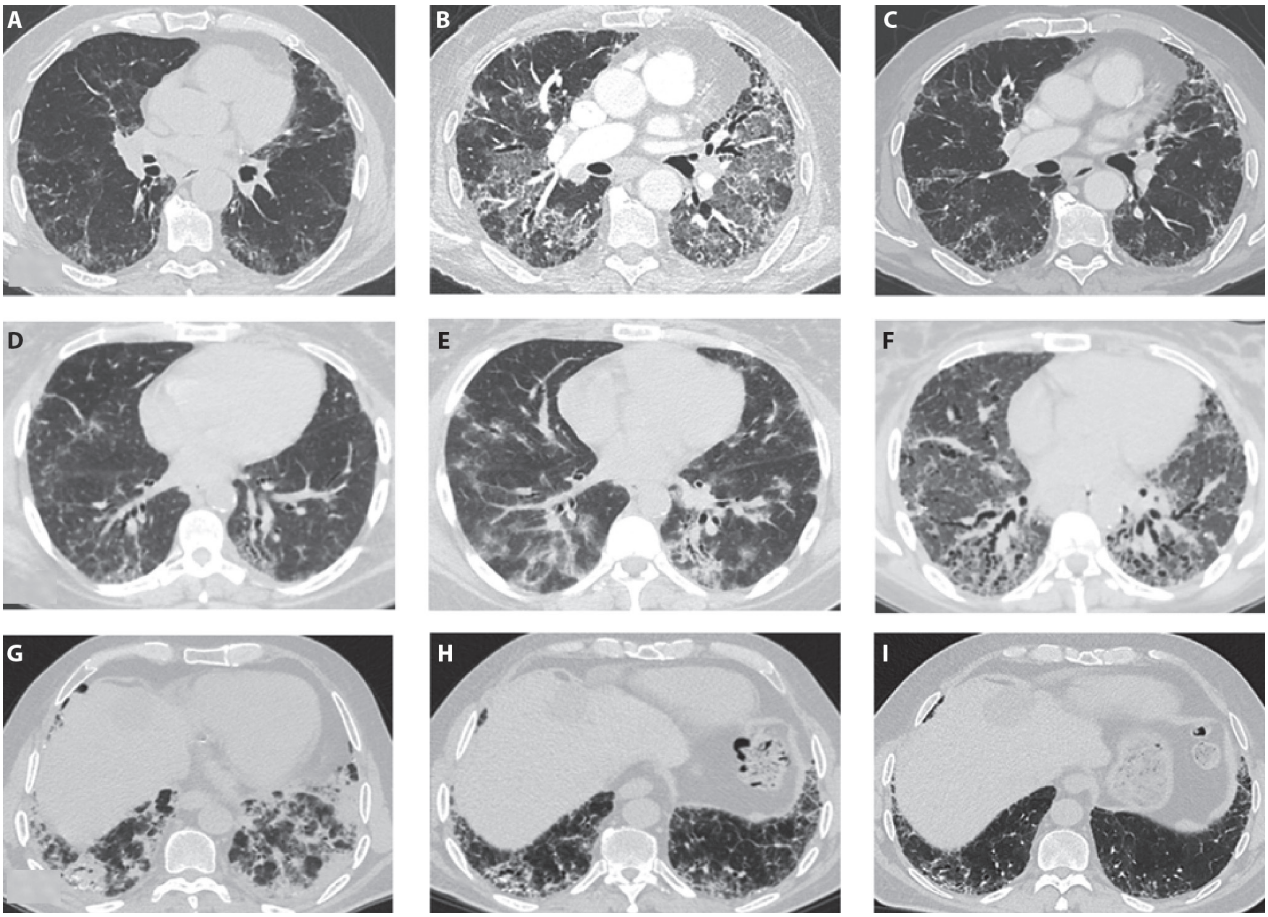

Figure 1. Clinical-radiological scenarios. ABC (Scenario 1); DEF (Scenario 2); GHI (Scenario 3).
Scenario 1: No COVID-19 impact on pre-existing ILD. Patient 1, male, 74y. A) HRCT (October 2021): Probable UIP pattern in IPF. B) CECT during COVID-19 (January 2022): Bilateral ground-glass opacities (GGOs) superimposed on fibrotic probable UIP pattern. C) HRCT post-COVID (December 2022): Complete resolution of GGOs; fibrotic ILD remains stable, despite the severe acute infection, with slight increase in fine reticulation.
Scenario 2: ILD progression after COVID-19. Patient 2, male, 65y. D) CT (May 2019): Fibrosing NSIP secondary to CTD (Sjogren's syndrome), with patchy subpleural GGOs and some traction bronchiectasis in both lungs. E) CT during COVID-19 (June 2020): Superimposed consolidations and diffuse GGOs. F) HRCT post-COVID (July 2021): Fibrotic progression of the CTD-ILD with volume loss, increased reticulations, and traction bronchiectasis.
Scenario 3: COVID-19 unmasks previously unknown ILD. Patient 3, male, 77y. G) HRCT at COVID-19 diagnosis (August 2024): Patchy consolidations and mild GGOs; subpleural reticulation and calcifications suggest underlying ILD. H) HRCT (October 2024): Consolidations decrease; subpleural reticulations and microcalcifications are more evident. I) HRCT post-COVID (March 2025): Resolution of infection-related findings; fibrosing ILD with probable UIP pattern now evident, leading to a multidisciplinary IPF diagnosis.

diagnoses, 4 (66.7%) presented with pneumonia and 2 (33.3%) with mild infection. Finally, all 5 (100%) COVID-19-related deaths occurred in patients who had pneumonia. In addition, 24 patients (8.7% of the remaining cohort, excluding COVID-19 deaths) died during the study. Out of these, 64% had IPF, and 58% had no history of SARS-CoV-2 infection. Causes of death included ILD progression (n = 19, 79%), pulmonary hypertension (n = 3, 12.5%), gastric cancer (n = 1), and pneumothorax (n = 1).

Five years after the onset of the SARS-CoV-2 pandemic, interest in its pulmonary *sequelae* has understandably declined. However, ILD patients - among other chronic respiratory conditions - have remained a focus of concern due to their perceived risk of disease progression [9]. This brief report aimed to provide a

real-world snapshot of clinical experiences during the early phase of healthcare resumption after pandemic restrictions were lifted. Our patient population had proactively adopted protective measures during the critical phases of the health crisis and showed high adherence to vaccination. This is reflected in the high proportion of pauci- or asymptomatic infections and a relatively low number of pneumonia cases - though mortality among these remained notable, partly due to incomplete vaccination and the complex clinical profiles of many patients. These outcomes should also be viewed in the context of reduced virulence of SARS-CoV-2 variants circulating between 2022 and 2023 (78% of infections), coinciding with the gradual achievement of herd immunity [1,2,10]. Together, these factors contributed to a clinical picture far removed from early worst-case projections. In fact, our study observed a notably high prevalence of SARS-CoV-2 infection within our ILD cohort compared to many previously published studies (probably due to the extended observation period and the widespread availability and accessibility of SARS-CoV-2 testing), but the clinical outcomes in our cohort were generally more favorable than those documented in initial pandemic waves [11,12,13], likely due to the high vaccination coverage, the herd immunity and the circulation of less virulent SARS-CoV-2 variants. While a direct causal link between SARS-CoV-2 and pulmonary fibrosis has largely been ruled out [3,4], ILD patients still warrant special attention. In those who developed pneumonia, distinguishing between *sequelae* of COVID-19 and progression of underlying ILD posed a significant clinical challenge. Accurate interpretation of radiologic findings required consideration of timing (resolution vs. persistence) and the type and distribution of new abnormalities to assess progression risk [8]. Another challenge was identifying subclinical ILD unmasked - but not caused - by SARS-CoV-2 infection. Overlooking this may lead to diagnostic errors, especially in non-specialized centers. Importantly, when excluding deaths due to COVID-19 pneumonia, overall mortality during the study did not significantly differ between patients with and without prior infection - suggesting similar clinical outcomes in both groups. The main limitations of our study are its retrospective nature and relatively small sample size, especially considering the broader relevance of the issue.

In conclusion, our findings suggest ILD patients demonstrated relative resilience to SARS-CoV-2 infection, supported by early precautionary measures, high vaccination rates, and structured follow-up. Although the infection had minimal impact on disease progression for most, distinguishing post-infectious changes from ILD progression remains a clinical challenge. Accurate radiologic assessment and early detection of subclinical ILD are essential. These findings reinforce the importance of specialized, long-term care to ensure precise diagnosis and tailored management in this vulnerable population.

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