Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
We conducted a study to examine the effect of COVID-19 on the acute exacerbation of interstitial lung disease (AE-ILD) early in the COVID-19 epidemic (January 1–April 30, 2020). An online questionnaire survey was conducted, which was completed by 134 hospitals. During this period, 854 patients with AE-ILD (including 12 cases of COVID-AE-idiopathic pulmonary fibrosis) were hospitalized at 128 hospitals. In comparison, the total number of AE-ILD hospitalizations during the same period in 2019 was 894. The number of hospitalizations increased at 17 hospitals, decreased at 27, and remained the same at 88 hospitals in 2020 compared to the same period in 2019. In 2020, COVID-19-related acute exacerbations had a significantly worse prognosis than non-COVID-19-related acute exacerbations in both 30-day and 90-day mortality. Because the prognosis of AE-ILD
1. Introduction

In 2020, infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing a disease known as COVID-19, has had a significant impact on medical care around the world. It is known that pneumonia in COVID-19 typically presents with bilateral ground glass-like shadows and can progress to acute respiratory failure, and in some cases, to acute respiratory distress syndrome [1]. Because viral infection is a well-known trigger for acute exacerbation of interstitial lung disease (AE-ILD) [2], COVID-19 may be expected to affect the frequency and prognosis of AE-ILD. Using an online questionnaire, we studied the frequency of AE-idiopathic pulmonary fibrosis (IPF) associated with COVID-19, and whether there was an overall increase or decrease in AE-ILD.

2. Material and methods

We conducted a study on AE-ILD early in the COVID-19 epidemic (January 1–April 30, 2020) to examine the effect of COVID-19 on the acute exacerbation of interstitial pneumonia. An online questionnaire survey was conducted with facilities accredited by the Japanese Respiratory Society (n = 705). Because COVID-19 pneumonia and AE-ILD are difficult to distinguish, those who fulfilled the criteria for AE and were COVID-19-positive were diagnosed as having COVID-19-related AE-ILD. The survey was completed in July–August 2020.

3. Results

Overall, 134 hospitals completed the online survey. From January 1 to April 30, 2020, there were 854 patients with AE-ILD (including 12 with COVID-AE-IPF, Table 1) who were hospitalized at 128 hospitals. In comparison, the total number of AE-ILD hospitalizations from January 1 to April 30, 2019 was 894. The number of hospitalizations increased at 17 hospitals, decreased at 27, and remained the same at 88 hospitals in 2020 compared to the same period in 2019; both time frames, therefore, were considered equivalent. In 2020, COVID-19-related acute exacerbations had a significantly worse prognosis than non-COVID-19-related acute exacerbations in both 30-day and 90-day mortality (p = 0.0071, p < 0.0001, respectively; Table 2).

4. Discussion

This study is the first report from the viewpoint of AE-ILD of COVID-19. The total number of AE-IPF cases from January to April 2020 was almost the same as the previous year. Although the frequency of COVID-19 in cases of acute exacerbations was extremely low at 1.4%, COVID-19-related AE-IPF had a poorer prognosis than non-COVID-19-related cases. The prevention measures for COVID-19, such as hand washing, wearing of face masks, and avoidance of the three Cs (closed spaces, crowded places, close-contact settings), are believed to have reduced the frequency of COVID-19 and COVID-19-related AE-IPF. In fact, the number of cumulative COVID-19 patients in April 30, 2020 reached 14,477 nationwide, of whom 415 died. The low frequency of COVID-19 in ILD is thought to be the effect of the small number of patients with COVID-19 in Japan and the effect of stringent infection control measures, especially for patients with lung disease who are afraid of acquiring COVID-19. Conversely, the reason why the frequency of acute exacerbations did not change despite the emergence of COVID-19 and the reduction of other respiratory infections may be explained by the fact that acute exacerbations can be caused by factors other than viral infection [3].

It is noteworthy that the 90-day mortality rate for acute exacerbations with COVID-19 was 75% (9/12), which was much higher than the non-COVID-19 90-day mortality rate (Table 1) [4]. This is even worse than the general COVID-19 respiratory failure mortality rate [5]. These results are compatible with the results of a recent study by Drake et al., who found that patients with ILD have a higher risk of death following COVID-19 than do matched patients without ILD [6].

There are several possible reasons for the poor prognosis of COVID-19 in ILD. Patients with ILD are presumed to have a worse prognosis than non-ILD patients because of reduced lung reserve and impaired gas exchange. In addition, increases in SARS-CoV-2 entry genes, such as angiotensin-converting enzyme-2 and baseline changes in interleukin-6 and type 1 interferon response genes in the cells of ILD patients, have been reported [7]; these could explain the poorer survival with COVID-19 related AE-ILD than with non-COVID-19 related AE-ILD. Finally, patients with ILD, especially IPF, have high levels of αvβ6 integrin in the alveolar epithelium, which is associated with a poor prognosis [8]; αvβ6 integrin also includes a binding site for the SARS-CoV-2 virus [9]. These findings can explain the poorer prognosis of COVID-19-related AE-ILD.

The 30- and 90-day mortality of AE-ILD in this study were much lower (15% and 16%, respectively) than the reported mortalities in previous studies, which ranged from 33% to 83% [4,10,11]. We are not sure of the reasons for this, but early detection and recently improved management, such as high-flow nasal cannula oxygen therapy, non-invasive ventilation, and pharmacologic therapy, including antibiotics, may have improved the outcomes [12]. In fact, recent clinical trials reported various lower mortality rates of AE-IPF: 7.1% and 61.2% in the INPULSIS® trials, 10.8% and 27.5% in a randomized controlled trial of thrombomodulin for AE-IPF [13,14].
This study has several limitations. First, because the survey was conducted through a retrospective, online-based survey, the results may have been affected by the personal bias of the survey participants. Second, this study was conducted in a single country (Japan) during a specific season, with a short observation period of 4 months. Third, the number of COVID-19-related AE-ILD cases was small (n = 12). There were 14,477 patients with COVID-19 nationwide, of whom 415 died, as of April 30, 2020. Therefore, the small number of COVID-19 cases in Japan at the time of study may have influenced the results. Finally, we did not evaluate COVID-19 in ILD conditions other than AE. Further studies are needed to evaluate the impact of COVID-19 on AE-ILD with a wider range and a larger number of patients during a longer period of observation.

### Table 1 – Characteristics of 12 patients with COVID-19 related AE-ILD.

| Age, years | Sex | Smoking | Diagnosis of ILD | Comorbidities | 30-day survival | 90-day survival |
|------------|-----|---------|------------------|---------------|----------------|---------------|
| 73         | Male| Ex      | NSIP             | HTN, Parkinson| Yes            | Yes           |
| 85         | Male| Never   | IPF              | HTN, Hyperlipidemia| Yes| No           |
| 83         | Male| Current | CPFE             | HTN, IHD      | Yes            | No            |
| 64         | Female| Unknown | CPFE             | Cerebral infarction, multiple sclerosis| Yes| Yes           |
| 69         | Female| Unknown | IPF              | Depression, prostate cancer treatment | No| No            |
| 78         | Male| Never   | IPF              | DM            | No             | No            |
| 68         | Male| Current | IPF              | DM            | No             | No            |
| 82         | Male| Never   | NSIP             | Dementia, cerebral infarction, after prostate cancer treatment | No| No            |
| 80         | Male| Ex      | NSIP             | HTN, DM, pleural mesothelioma| Yes| Yes           |
| 72         | Male| Current | CPFE             | DM, | No| No            |
| 73         | Male| Ex      | RA-IID           | RA            | Yes            | No            |
| 73         | Male| Ex      | IPF              | HTN           | Yes            | No            |

Abbreviations: ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; IPF, idiopathic pulmonary fibrosis, CPFE, combined pulmonary fibrosis with emphysema; RA-IID, ILD associated with rheumatoid arthritis; HTN, hypertension; IHD, ischemic heart disease; DM, diabetes mellitus.

### Table 2 – Outcomes of acute exacerbation of interstitial lung disease by COVID-19.

|                      | COVID-19-related AE | Non-COVID-19-related AE | p-value |
|----------------------|---------------------|-------------------------|---------|
| Total, n             | 12                  | 842                     |         |
| 30-day mortality, n (%) | 6 (50%)            | 129 (15%)               | 0.0071  |
| 90-day mortality, n (%) | 9 (75%)            | 136 (16%)               | <0.0001 |

AE, acute exacerbation.

In conclusion, the total number of AE-IPF cases was similar before and after the start of the COVID-19 pandemic. Because the prognosis of AE-IPF associated with COVID-19 is extremely poor despite the low frequency of occurrence, prevention of COVID-19 is especially important for ILD patients.

### References

1. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguín-Rivera Y, Escalera-Anteza JP, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Trav Med Infect Dis 2020;34:101623. Electronic address: https://www.lancovid.org.
2. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. Am J Respir Crit Care Med 2016;194(3):265-75.
3. Wootton SC, Kim DS, Kondoh Y, Chen E, Lee JS, Song JW, et al. Viral infection in acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;183(12):1698-702.
4. Suzuki A, Kondoh Y, Brown KK, Johkoh T, Kataoka K, Fukuoja J, et al. Acute exacerbations of fibrotic interstitial lung diseases. Respirology 2020;25(5):525–34.
5. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. RECOVERY Collaborative group. N Engl J Med 2020;NEJMo2021436. https://doi.org/10.1056/ NEJMo2021436.
6. Drake TM, Docherty AB, Harrison EM, Quint JK, Adamahi H, Agnew S, et al. ISARIC4C Investigators. Outcome of hospitalization for COVID-19 in patients with interstitial lung disease. An international multicenter study. Am J Respir Crit Care Med 2020;202(12):1656–65.
7. Bui LT, Winters NI, Chung MI, Joseph C, Gutierrez AJ, Habermann AC, et al. Single-cell RNA-sequencing reveals dysregulation of molecular programs associated with SARS-CoV-2 severity and outcomes in patients with chronic lung disease. the Human Cell Atlas Lung Biological Network bioRxiv 2020:347187. 10.20.

### Conflict of Interest

The authors have no conflicts of interest to declare for this article.

This study was partially supported by the Study Group on Diffuse Lung Disease, Scientific Research/Research on Intractable Diseases in the Ministry of Health, Labor and Welfare, Japan.

This study has several limitations. First, because the survey was conducted through a retrospective, online-based survey, the results may have been affected by the personal bias of the survey participants. Second, this study was conducted in a single country (Japan) during a specific season, with a short observation period of 4 months. Third, the number of COVID-19-related AE-ILD cases was small (n = 12). There were 14,477 patients with COVID-19 nationwide, of whom 415 died, as of April 30, 2020. Therefore, the small number of COVID-19 cases in Japan at the time of study may have influenced the results. Finally, we did not evaluate COVID-19 in ILD conditions other than AE. Further studies are needed to evaluate the impact of COVID-19 on AE-ILD with a wider range and a larger number of patients during a longer period of observation.
[8] Saini G, Porte J, Weinreb PH, Violette SM, Wallace WA, McKeever TM, et al. αvβ6 integrin may be a potential prognostic biomarker in interstitial lung disease. Eur Respir J 2015;46(2):486–94.

[9] Sigrist C, Bridge A, Le Mercier P. A potential role for integrins in host cell entry by SARS-CoV-2. Antivir Res 2020 May;177:104759.

[10] Agarwal R, Jindal SK. Acute exacerbation of idiopathic pulmonary fibrosis: a systematic review. Eur J Intern Med 2008;19:227–35.

[11] Kolb M, Bondue B, Pesci A, Miyazaki Y, Song JW, Bhatt NY, et al. Acute exacerbations of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018;27:180071.

[12] Kondoh Y, Cottin V, Brown KK. Recent lessons learned in the management of acute exacerbation of idiopathic pulmonary fibrosis. Eur Respir Rev 2017;26:170050.

[13] Kreuter M, Koegler H, Trampisch M, Geier S, Richeldi L. Differing severities of acute exacerbations of idiopathic pulmonary fibrosis (IPF): insights from the INPULSIS trials. Respir Res 2019;20:71.

[14] Kondoh Y, Azuma A, Inoue Y, Ogura T, Sakamoto S, Tsushima K, et al. Thrombomodulin alfa for acute exacerbation of idiopathic pulmonary fibrosis. A randomized, double-blind placebo-controlled trial. Am J Respir Crit Care Med 2020;201:1110–9.