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Rapid Communication

COVID-19 and acute exacerbation of interstitial lung disease

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ARTICLE INFO

Article history:
Received 9 April 2021
Received in revised form
3 June 2021
Accepted 14 June 2021
Available online 30 June 2021

Keywords:
COVID-19
Acute exacerbation

ABSTRACT

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

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https://doi.org/10.1016/j.resinv.2021.06.007
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Idiopathic pulmonary fibrosis
Interstitial lung disease

associated with COVID-19 is extremely poor, prevention of COVID-19 is especially important for patients with ILD.

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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 C's (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 antifibrotics, 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].

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,	No	No
78	Male	Never	IPF	No	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-ILD, 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.

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.

5. Conclusions

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.

Support statement

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.

Conflict of Interest

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

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