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# Incidence of acute exacerbation in patients with interstitial lung disease after COVID-19 vaccination

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ABSTRACT

Acute exacerbations due to COVID-19 vaccination in patients with interstitial lung disease (ILD) have been reported, but their incidence is unknown. We investigated the incidence of exacerbations of ILD and respiratory symptoms due to the mRNA COVID-19 vaccines. A questionnaire survey was conducted on adverse reactions to the mRNA COVID-19 vaccination in 545 patients with ILD attending our hospital and retrospectively examined whether the eligible patients actually developed acute exacerbations of ILD induced by the vaccine. Of the 545 patients, 17 (3.1%) patients were aware of the exacerbation of respiratory symptoms, and four (0.7%) patients developed an acute ILD exacerbation after vaccination. Of the four patients who experienced exacerbations, two had collagen vascular disease-associated ILD, one had nonspecific interstitial pneumonia, another had unclassifiable idiopathic pneumonia, and none had idiopathic pulmonary fibrosis. Four patients were treated using steroid pulse therapy with a steroid taper, and two of the four also received intravenous cyclophosphamide pulse therapy. Tacrolimus was started in one patient with myositis-associated interstitial lung disease. Eventually, all patients exhibited improvement with immunosuppressive treatment and were discharged. COVID-19 vaccination for patients with ILD should be noted for developing acute exacerbations of ILD with low incidence, although manageable with early diagnosis and treatment.

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a disease that causes acute respiratory illness and is spreading worldwide. Symptoms of COVID-19 range from asymptomatic to fatal with severe acute respiratory syndrome. Alternatively, vaccines against COVID-19, proven to be highly effective and well-tolerated have been rapidly developed [1–3], and two or more doses of these COVID-19 vaccines have been promoted in several countries. However, in the real world, some patients and physicians are concerned about the safety of these vaccines. This is a particularly crucial issue in patients with interstitial lung disease (ILD) because while ILD is a risk factor for COVID-19 severity, the development or acute exacerbation of ILD (AE-ILD) after the COVID-19 vaccination has actually been reported [4–7]. So far, there have been only a few reports of the development or ILD exacerbations after COVID-19 vaccination, and the incidence of acute exacerbation after COVID-19 vaccination in patients with ILD in clinical practice remains unclear. The incidence of all adverse reactions to the COVID-19 vaccines in these patients is also unknown. Thus, we investigated the incidence of adverse reactions after COVID-19 vaccination in ILD patients, including AE-ILD.

## 2. Methods

This retrospective study was conducted from April to December 2021 at the Kanagawa Cardiovascular and Respiratory Center according to the ethical principles of the 1964 Helsinki Declaration and subsequent amendments. All procedures were approved by the Ethics Committee of the Kanagawa Cardiovascular and Respiratory Center (approval number KCRC-21-0006). Consecutive patients with ILD attending the outpatient clinic of ILD specialists at the hospital who have completed 2 doses of SARS-CoV-2 or discontinued after 1 dose due to adverse effects and agreed to complete the questionnaire for adverse reactions to the

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vaccines were included. First, eligible patients were asked to complete a questionnaire about the adverse reactions of the COVID-19 vaccine within 6 months of vaccination. Questionnaire survey items were as follows: 1) Type of COVID-19 vaccine received, 2) Date of vaccination, 3) Adverse reactions to the COVID-19 vaccine (multiple-choice format), 4) The presence or absence of exacerbations of respiratory symptoms after COVID-19 vaccination and if so, details of their exacerbations (descriptive format). Next, patients' clinical background and whether or not their ILD was exacerbated after the COVID-19 vaccination was obtained from their medical records. In cases where the patients had developed AE-ILD after COVID-19 vaccination, detailed patient background, treatment course, and outcomes of the acute exacerbation were also obtained. AE-ILD in relation to COVID-19 vaccination was defined as worsening of respiratory symptoms owing to COVID-19 vaccination, with worsening of oxygenation and appearance of new ground grass opacity/consolidation on computed tomography (CT) not because of pulmonary edema or other causes within one month after vaccination, referring to the acute exacerbation of idiopathic pulmonary fibrosis (IPF) criteria suggested by the international working group in 2016 [8]. The eligible patients were classified into two groups: those who reported worsening respiratory symptoms because of COVID-19 vaccination (the deterioration group) and those who reported no worsening of respiratory symptoms after COVID-19 vaccination (the stable group), and a comparative analysis was conducted between the two groups regarding differences in all adverse reactions to the COVID-19 vaccine, types and ILD treatment. All statistical analyses were conducted using JMP® pro 13.2.0 software (SAS Institute Inc. Cary, NC, USA). Fisher's exact test was used for categorical data, and the Mann-Whitney *U* test was used for continuous data. A *p*-value of $<0.05$ was considered statistically significant for all analyses.

## 3. Results

Five hundred and forty-five patients with ILD who have received the COVID-19 vaccine responded to the survey. All but one patient who developed AE-ILD after first dose of the COVID-19 vaccine had received two doses. Of the 545 patients, 17 (3.1%) reported that COVID-19 vaccination caused an adverse reaction of worsening respiratory symptoms (classified as the deterioration group), and the remaining 528 patients remained unchanged (classified as the stable group). Regarding adverse reactions related to respiratory symptoms in the deterioration group, coughing the most common (14/17, 82.4%), followed by dyspnea (8/17, 47.1%) and increased sputum (2/17, 11.8%). Patients' characteristics, including the vaccine type and treatment of ILD, are shown in Table 1. The deterioration group tended to be younger than the stable group, but there were insignificant sex differences. The type of ILD in the deterioration group included nonspecific interstitial pneumonia (NSIP) and collagen vascular disease-associated ILD (CVD-ILD) more frequently, with no IPF. Although there were no significant differences between the two groups regarding the baseline ILD treatment, the use of long-term oxygen therapy tended to be more common in the deterioration group.

The common adverse reactions other than respiratory symptoms due to COVID-19 vaccines are indicated in Table 2. Adverse reactions other than respiratory symptoms were observed to be significantly higher in the deterioration group than in the stable group (94.1% in the deterioration group vs. 52.1% in the stable group, $p < 0.001$). The most common adverse reaction was fatigue in both groups (70.6% in the deterioration group and 29.9% in the stable group, $p < 0.001$), followed by headache (52.9%), fever (47.1%) in the deterioration group, and muscle pain (22.5%) and fever (15.3%) in the stable group. All adverse reactions were more common in the deterioration group than in the stable group, and several of these varied statistically. Furthermore, significantly more patients in the deterioration group had two or more adverse reactions than those in the stable group (76.5% in the deterioration group vs. 26.1% in the stable group, $p < 0.001$). Four of the total 545 cases (0.7%) or 17.6% of the deterioration group developed AE-ILD in relation to COVID-19 vaccination. The clinical course of these four cases is shown in Table 3. Of the four cases, two were CVD-ILD (myositis-associated ILD), one was NSIP, and the other was unclassifiable idiopathic interstitial pneumonia. No obvious cause of acute exacerbation other than COVID-19 vaccination was identified in any of the four cases. The baseline percent predicted forced vital capacity (%FVC) and percent predicted diffusing capacity of carbon monoxide (%DLCO) were markedly low. Baseline KL-6 was elevated in all patients, and honeycomb on CT was found in two of four patients. All patients were hospitalized and received steroid pulse therapy (intravenous methylprednisolone 500-mg for three days) with steroid taper. Two of the four patients also received intravenous cyclophosphamide pulse therapy, and tacrolimus was

**Table 1**
Patients' characteristics in this study.

| | All patients (n = 545) | Stable group (n = 528) | Deterioration group (n = 17) |
|---|---|---|---|
| Age, median [range] | 72 [22–91] | 72 [22–91] | 64 [40–84] |
| Male, n (%) | 314 (58%) | 304 (58%) | 10 (59%) |
| Type of vaccine | | | |
| BNT162b2 (BioNTech/Pfizer) | 478 (87.7%) | 461 (87.3%) | 17 (100%) |
| mRNA-1273 (Moderna) | 53 (9.7%) | 53 (10.0%) | 0 |
| unknown | 14 (2.6%) | 14 (2.7%) | 0 |
| Type of ILD | | | |
| IPF | 122 (22.4%) | 122 (23.1%) | 0 |
| NSIP | 34 (6.2%) | 31 (5.9%) | 3 (17.6%) |
| COP | 11 (2.0%) | 11 (2.1%) | 0 |
| PPFE | 18 (3.3%) | 17 (3.2%) | 1 (5.9%) |
| RB-ILD | 3 (0.6%) | 3 (0.6%) | 0 |
| unclassifiable IP | 177 (32.5%) | 173 (32.8%) | 4 (23.5%) |
| CVD-ILD | 120 (22.0%) | 113 (21.4%) | 7 (41.2%) |
| HP | 43 (7.9%) | 41 (7.8%) | 2 (11.8%) |
| Other | 17 (3.1%) | 17 (3.2%) | 0 |
| Treatment for ILD | | | |
| Steroid | 167 (30.6%) | 161 (30.5%) | 6 (35.3%) |
| Immunosuppressant | 117 (21.5%) | 113 (21.4%) | 5 (29.4%) |
| Nintedanib | 52 (9.5%) | 49 (9.3%) | 3 (17.6%) |
| Pirfenidone | 60 (11.0%) | 58 (11.0%) | 2 (11.8%) |
| Supplemental oxygen | 63 (11.6%) | 59 (11.2%) | 4 (23.5%) |

Abbreviations: ILD: interstitial lung disease, IPF: idiopathic pulmonary fibrosis, NSIP: nonspecific interstitial pneumonia, COP: cryptogenic organizing pneumonia, PPFE: pleuroparenchymal fibroelastosis, RB-ILD: respiratory bronchiolitis-interstitial lung disease, IP: idiopathic pneumonia, CVD-ILD: collagen vascular disease-associated interstitial lung disease, HP: hypersensitivity pneumonia.

**Table 2**
Adverse reactions other than respiratory symptoms to COVID-19 vaccination in patients with interstitial lung disease in this study.

| | All patients (n = 545) | Stable group (n = 528) | Deterioration group (n = 17) | P |
|---|---|---|---|---|
| Fever | 89 (16.3%) | 81 (15.3%) | 8 (47.1%) | 0.002 |
| 37.5–37.9° | 45 (8.3%) | 42 (8.0%) | 3 (17.7%) | 0.158 |
| 38.0°< | 48 (8.8%) | 42 (8.0%) | 6 (35.3%) | 0.002 |
| Fatigue | 170 (31.2%) | 158 (29.9%) | 12 (70.6%) | <0.001 |
| Headache | 65 (11.9%) | 56 (10.6%) | 9 (52.9%) | <0.001 |
| Chill | 23 (4.2%) | 20 (3.8%) | 3 (17.7%) | 0.030 |
| Nausea | 12 (2.2%) | 10 (1.9%) | 2 (11.8%) | 0.050 |
| Diarrhea | 12 (2.2%) | 11 (2.1%) | 1 (5.9%) | 0.31 |
| Muscle pain | 126 (23.1%) | 119 (22.5%) | 7 (41.2%) | 0.082 |
| Arthralgia | 40 (7.3%) | 35 (6.6%) | 5 (29.4%) | 0.005 |
| Rash | 23 (4.2%) | 21 (4.0%) | 2 (11.8%) | 0.157 |
| Any adverse effects | 291 (53.4%) | 275 (52.1%) | 16 (94.1%) | <0.001 |
| >2 adverse effects | 151 (27.7%) | 138 (26.1%) | 13 (76.5%) | <0.001 |
| No adverse effect | 254 (46.6%) | 253 (47.9%) | 1 (5.9%) | |

Footnote: Describing adverse reactions that appeared in any of vaccinations.

**Table 3**
Cases of acute exacerbations of interstitial lung disease in relation to COVID-19 vaccination.

| Case* | Age | Sex | BMI | Type of ILD | Date of admission | Prior treatment | Baseline data | | | | Other adverse reactions | Maximum oxygen administration | Treatment for AE-ILD | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | % FVC† | % DLCO‡ | KL-6 | Honeycomb on HRCT | | | | |
| 1 | 60 | M | 28.7 | CVD-ILD | 19 days after 1st vaccination | none | NA | NA | NA | no | fever, cough, dyspnea | $FiO_2$ 80% in HFNC | mPSL pulse + IVCY + Tac | improve |
| 2 | 43 | M | 25.6 | NSIP | 21 days after 2nd vaccination | PSL, Tac | 42.2 | 40.0 | 2006 | yes | fever, fatigue, dyspnea | 3L/min | mPSL pulse + IVCY | improve |
| 3 | 62 | M | 22.3 | CVD-ILD | 17 days after 2nd vaccination | PSL, Tac, LTOT | 56.5 | 25.6 | 4233 | no | fever, fatigue, headache, chill, arthralgia, dyspnea | 7L/min | mPSL pulse | improve |
| 4 | 73 | M | 29.9 | unclassifiable IP | 30 days after 2nd vaccination | PFD, PSL, LTOT | 51.0 | 37.9 | 1616 | yes | nausea, cough | 7L/min | mPSL pulse | improve |

Abbreviations and footnote: *all patients received the BNT162B2 (BioNTech/Pfizer) vaccine. †‡most recent data available for reference. BMI: body mass index, ILD: interstitial lung disease, CVD: collagen vascular disease, NSIP: nonspecific interstitial pneumonia, PSL: prednisolone, Tac: tacrolimus, LTOT: long-term oxygen therapy, %FVC: percent predicted forced vital capacity, %DLCO: percent predicted diffuse capacity of the lung for carbon monoxide, NA: not available, HRCT: high resolution computed tomography, HFNC: high-flow nasal cannula, AE: acute exacerbation, mPSL: methylprednisolone, IVCY: intravenous cyclophosphamide.

started in one patient with myositis-associated ILD. Eventually, all patients responded to immunosuppressive treatment and were discharged with improvement.

## 4. Discussion

This study evaluated the incidence of adverse reactions to the COVID-19 vaccine, including AE-ILD, in patients with ILD. The primary finding of this study is that 17 (3.1%) of the 545 patients with ILD experienced an exacerbation of respiratory symptoms after the COVID-19 vaccination and that four patients (0.7%) actually developed AE-ILD related to COVID-19 vaccination. In IPF, acute exacerbations are thought to be relatively common, with a reported annual incidence of 4%–19% [8]. Additionally, it has been reported that acute exacerbations can occur in ILD other than IPF, with a reported incidence of 4.2% per year in NSIP and 1.25%–3.3% per year in CVD-ILD [9]. Although the etiology and mechanism of AE-ILD are still poorly understood, it is thought that viral infection, aspiration, air pollution, mechanical stress, or drugs may work to accelerate fibrosis and trigger acute exacerbations [8]. Although it has not been determined whether vaccines can trigger acute exacerbations in patients with ILD, several cases of suspected AE-ILD caused by influenza or COVID-19 vaccines have been reported [6,10,11]. A possible mechanism of AE-ILD by mRNA vaccines like BNT162b2 (BionTech/Pfizer) or mRNA-1273 (Moderna) coding for the SARS-CoV-2 full-length spike protein could be due to an autoimmune response. Molecular mimicry between the spike protein of SARS-CoV-2 and the human Proteome has been proposed, and it has been indicated that SARS-CoV-2 spike protein antibody reacts strongly with human tissue antigens, such as transglutaminase 3, transglutaminase 2, anti-extractable nucleolar antigen, and mitochondria [12,13]. Additionally, it has been reported that peptides are shared between spike glycoproteins from SARS-CoV-2 and human surfactant-related proteins [14]. The activation of cellular immunity or cross-reactivity between vaccine-encoded SARS-CoV-2 spike protein and human tissue might trigger AE-ILD related to COVID-19 vaccination. Interestingly, of the four patients who experienced exacerbations, two had CVD-ILD, and another had NSIP with positive anti-cyclic citrullinated peptide (anti-CCP) antibodies and was considered to have autoimmune characteristics, and none had IPF. Considering these findings, AE-ILD related to COVID-19 vaccination may be more likely to occur in autoimmune disease-related ILD, such as CVD-ILD, unlike idiopathic interstitial pneumonia, which would likely occur in IPF. However, note that these hypotheses are only speculative, as the autoimmune response has not been directly proven involved in AE-ILD related to COVID-19 vaccination. In addition, three of the four cases for which pulmonary function data were available had a markedly low pulmonary function. Thus, low pulmonary function and the appearance of respiratory adverse reactions from COVID-19 vaccination may be risk factors for AE-ILD development related to COVID-19 vaccination. Another finding of this study is that, as indicated in Table 2, the incidence of all adverse reactions to the COVID-19 vaccines other than respiratory symptoms did not appear to be any clearly higher in patients with ILD than previously reported from clinical trials [1,2], although the age and background of the population were different and cannot be simply compared. This means that in most patients with ILD, the COVID-19 vaccines can be safely administered. Given that ILD is a risk factor for COVID-19 severity, COVID-19 vaccination is still recommended for patients with ILD, even considering the much lower incidence of developing AE. Further studies to identify patients more likely to develop AE-ILD due to vaccination are required.

This study has some limitations. First this is a retrospective study at a single center. The actual adverse reactions to COVID-19 vaccines may slightly differ because the questionnaire survey was conducted sometime after the vaccination. Second, the possibility that the AE-ILD reported in this study was caused by factors other than COVID-19 vaccination has not been completely ruled out. Triggers for AE-ILD are often difficult to identify and may be caused by viral infections that are

difficult to diagnose. However, based on the clinical course and the absence of any other apparent causes after searching as much as possible, it was considered that the cases in this study were AE-ILD related to COVID-19 vaccination. As this study included only four patients who developed AE-ILD and was unable to identify the risk factors to develop AE-ILD after vaccination, further large-scale investigation is required.

In conclusion, COVID-19 vaccination in patients with ILD can cause AE-ILD in less than 1% and should be administered with caution. Particular attention may be needed in patients with pulmonary function impairment or autoimmune disease-related ILD. Most ILD patients benefit the vaccination with low incidence of AE-ILD which, even if occur, is manageable with early diagnosis and treatment.

## Author contributions

MS had full access to all of the data in the study and responsibility for its integrity and the accuracy of the data analysis. MS, TB, AS and TO contributed to the study concept and design. MS and EH drafted the manuscript. MS, HK, SI, ET and TO contributed to data collection. MS, ET, SY and KF contributed to data analysis. All authors revised the manuscript critically for important intellectual content and approved the final manuscript.

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