# Does COVID-19 vaccination increase the risk of interstitial lung disease at a population level?



Received: 14 Nov 2023
Accepted: 5 Jan 2024

*To the Editor:*

The coronavirus disease of 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread worldwide, with over 675 million individuals infected to date. The clinical course of the infection showed a wide range of severity, from asymptomatic cases to severe pneumonia with multiorgan failure requiring intensive care [1]. Many individuals recovering from COVID-19 continue to face long-term conditions, including persistent respiratory symptoms [2] and impaired pulmonary function [3]. Among these, post-COVID-19 interstitial lung disease (ILD) is one of the most severe complications. Myall *et al*. reported that 7% of patients had inflammatory ILD on chest computed tomography (CT) six weeks after hospital discharge [4].

In this situation, vaccination against COVID-19 has been thought to play a crucial role in preventing post-COVID-19 ILD by preventing severe cases of COVID-19 [5] and long COVID [6]. On the other hand, some recent case reports [7–9] documented patients who developed respiratory symptoms and radiographic changes indicative of ILD shortly after receiving COVID-19 vaccination. While these reports are limited in number, they suggest a temporal association that warrants further investigation. The multicentre survey [10] collated data from several healthcare centres that indicated a small but notable incidence of ILD in individuals following COVID-19 vaccination. Although these findings do not establish a causal relationship, they highlight the need for ongoing surveillance and detailed examination of potential vaccine-related adverse events, particularly in the context of respiratory diseases like ILD. In this study, using a nationwide database, we aimed to compare the incidence and risk of ILD in individuals who were vaccinated for COVID-19 and in propensity-score matching individuals who were not vaccinated for COVID-19.

A retrospective cohort study was conducted using data from the Korean National Health Insurance Service (NHIS). In Korea, this single-payer universal health system covers about 97% of all Korean citizens and contains claims data on all use of medical facilities, including International Classification of Diseases, 10th revision (ICD-10) codes. This study was approved by the Institutional Review Board of Hallym University Kangnam Sacred Heart Hospital (institutional review boards no. 2023–03–022). The review board waived the requirement for written informed consent because the data were public and anonymised under confidentiality guidelines.

To establish COVID-19-naïve/COVID-19 vaccinated and unvaccinated groups, we used the NHIS SARS-CoV-2 database consisting of claims-based data for patients diagnosed with COVID-19 (COVID-19 cohort) and those who were not diagnosed with COVID-19 (control cohort) between 8 October, 2020 and 31 December, 2021 (n=8 463 712). The study commenced with 7 199 933 individuals with age >20 years from 1 January, 2020, to 31 December, 2021. From this population, 476 656 were excluded due to at least one recorded SARS-CoV-2 infection, leaving 6 723 277 individuals. This cohort was then divided into 6 148 749 subjects with vaccinations and 574 528 subjects without. As shown in Supplementary figure 1, after exclusion of subjects not eligible to our study, the final cohorts consisted of 554 072 vaccinated individuals and 554 072 controls without vaccination. Participants were followed-up for ten months. The outcome of interest was ILD diagnosis based on claims data from NHIS. We compared the incidence of ILD between vaccinated and unvaccinated individuals. ILD was defined using ICD-10 codes (J84.x, J67,

Shareable abstract (@ERSpublications)
**This study showed a significantly lower incidence of ILD among COVID-19 vaccinated individuals compared to unvaccinated, suggesting that the risk of COVID-19 vaccine-related ILD is not as high as previously reported** https://bit.ly/3TWzzxP

**Cite this article as:** Kim T, Lee H, Jeong CY, *et al*. Does COVID-19 vaccination increase the risk of interstitial lung disease at a population level?. *ERJ Open Res* 2024; 10: 00690-2023 [DOI: 10.1183/23120541.00690-2023].

J70 and D86), and comorbidities were defined based on a combination of past medical history, ICD-10 codes and drug prescriptions [11]. Connective tissue disorder (CTD)-related ILD was defined as ICD-10 codes for ILD with ICD-10 codes for CTD (M05, M06, M32, M33, M34, M315, M350, M351, M353, M359 and M360). Otherwise, ILD was regarded as non-CTD ILDs, which was further classified into idiopathic pulmonary fibrosis (J84.1), hypersensitivity pneumonitis (J67) and sarcoidosis (D86). We also identified lymphangioleiomyomatosis and Langerhans cell histiocytosis (J84.8), pulmonary alveolar proteinosis (J84.0), cryptogenic organising pneumonia (J84.18) and drug induced ILD (J70.4). We compared the cumulative incidence rate of CTD-related and non-CTD-related ILD between COVID-19 vaccinated and unvaccinated individuals using log-rank test. Cox proportional hazard regression analysis was used to estimate the hazard ratio for developing ILD in vaccinated *versus* unvaccinated individuals. A two-sided $p<0.05$ was considered significant.

The mean age of the vaccinated group was 45.3±17.4 years, and that of the unvaccinated group was 45.7 ±18.1 years. Males represented 49.5% of both unvaccinated and vaccinated group. During a follow-up period of ten months, 3.6% (398 out of 1 108 144) of participants developed ILD. The incidence rate of ILD was lower in the vaccinated group than among controls (6.8 out of 1,000 *versus* 10.6 out of 1000 person-years, $p<0.0001$). Similarly, there was a significant intergroup difference in the cumulative incidence rate for ILD development (log-rank test, $p<0.001$) (figure 1a). The hazards for developing ILD were lower among the vaccinated group than among controls (adjusted hazard ratio (aHR), 0.64; 95% confidence interval (CI), 0.52–0.78). Similarly, the vaccinated group showed a significantly lower incidence in both the CTD-related ILD (29 cases *versus* 61 cases, $p<0.001$) and the non-CTD-related ILD (128 cases *versus* 180 cases, $p=0.002$). Furthermore, when comparing the incidence and risk of ILD in vaccinated and unvaccinated subjects, significant differences were found by age, sex, residence region, economic status and comorbidities (figure 1b).

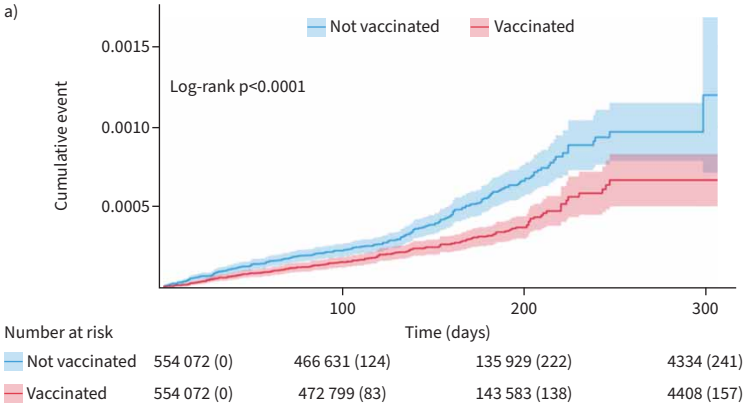
Findings showed a notably lower ILD incidence in vaccinated individuals, contradicting previous concerns about a high correlation between ILD and COVID-19 vaccination from prior case studies. Surprisingly, it found that COVID-19 vaccination was associated with a reduced ILD risk, suggesting a potentially protective role against ILD. However, this does not imply the vaccine directly prevents ILD. It is more plausible that the COVID-19 vaccine might protect against ILD following an undetected SARS-CoV-2 infection. Vaccinated individuals likely exhibited fewer and less severe symptoms, thus were less likely to be tested and diagnosed for COVID-19. This suggests a higher proportion of asymptomatic or mildly symptomatic SARS-CoV-2 infections among vaccinated individuals, where the vaccine may have helped prevent subsequent ILD.

COVID-19 vaccination could protect against ILD by stimulating immune responses against SARS-CoV-2 [12]. Given that severe COVID-19 can lead to lung damage and potentially ILD [4], the vaccine, by mitigating severe COVID-19, might lower the risk of ILD. The vaccine could also potentially limit lung inflammation, a key factor in ILD development, in individuals infected with SARS-CoV-2. Vaccination prepares the immune system to effectively respond to specific pathogens, so vaccinated people potentially have the capacity to defend SARS-CoV-2 and reduce the severity of the infection and associated lung inflammation. In contrast, unvaccinated individuals may not have enough capacity to defend SARS-CoV-2, which can lead to more severe lung inflammation and COVID-19 complications. Several studies [5, 13] have reported a reduced risk of severe COVID-19, hospitalisation and mortality in vaccinated individuals compared to unvaccinated. While the extent to which vaccination can reduce lung inflammation may vary depending on individual factors, vaccination is an important tool in reducing the overall burden of COVID-19 and its associated complications. Additionally, an oral COVID-19 vaccine was found to protect hamsters from severe COVID-19, resulting in less alveolar damage compared to unvaccinated hamsters [14]. However, more research is necessary to fully understand the relationship between COVID-19 vaccines and ILD, as factors such as genetic predisposition, pre-existing conditions, environmental exposures and drug interactions may also influence this relationship.

We acknowledge that this study has several limitations. First, since the diagnosis of COVID-19 was based on ICD-10 codes, patients who were infected but not diagnosed at the hospital may have been included. Second, diagnosis of ILD was also based on the ICD-10 code without CT scan data. Third, the study was conducted in a single country, potentially limiting the generalisability of the results to other regions with differing conditions. Fourth, although our study provides preliminary evidence as the first epidemiological study that may diminish concerns of COVID-19 vaccination causing ILD, our data do not imply that COVID-19 vaccination does not cause ILD since we evaluated this issue at a population level. Therefore, further prospective studies are needed to confirm these findings.

https://doi.org/10.1183/23120541.00690-2023

a)




b)

| | | Number of event | | IR (out of 1000 PY) | | Unadjusted HR (95% CI) | p-value |
|---|---|---|---|---|---|---|---|
| | | Not vaccinated (N=554 072) | Vaccinated (N=554 072) | Not vaccinated (N=554 072) | Vaccinated (N=554 072) | | |
| Age, years | | | | | | | |
| >60 | | 44/426 298 | 19/426 109 | 2.8 | 1.2 | 0.43 (0.25–0.74) | 0.003 |
| 60–69 | | 67/64 766 | 29/64 817 | 19.4 | 8.2 | 0.43 (0.28–0.66) | <0.001 |
| ≥70 | | 130/63 008 | 109/63 146 | 37.2 | 28.9 | 0.78 (0.60–1.01) | 0.048 |
| Sex | | | | | | | |
| Female | | 105/280 028 | 67/280 013 | 9.0 | 5.6 | 0.62 (0.46–0.85) | 0.002 |
| Male | | 136/274 044 | 90/274 058 | 12.4 | 8.1 | 0.65 (0.50–0.85) | <0.001 |
| Residence region | | | | | | | |
| Rural | | 26/34 573 | 18/34 618 | 17.0 | 11.4 | 0.67 (0.36–1.21) | 0.143 |
| Small town | | 50/124 641 | 47/124 595 | 9.7 | 9.0 | 0.91 (0.61–1.36) | 0.527 |
| Metropolitan | | 165/394 858 | 92/394 859 | 10.3 | 5.7 | 0.55 (0.42–0.71) | <0.001 |
| Economic state | | | | | | | |
| Low | | 63/136 630 | 43/136 618 | 11.3 | 7.5 | 0.66 (0.36–1.21) | 0.026 |
| Middle | | 96/273 142 | 56/273 157 | 8.8 | 5.1 | 0.57 (0.41–0.80) | 0.001 |
| High | | 82/144 300 | 58/144 297 | 13.4 | 9.3 | 0.69 (0.49–0.91) | 0.018 |
| Comorbidities | | | | | | | |
| Hypertension | No | 166/491 133 | 109/491 208 | 8.5 | 5.5 | 0.65 (0.51–0.82) | 0.005 |
| | Yes | 75/62 939 | 48/62 864 | 23.9 | 14.6 | 0.61 (0.42–0.88) | |
| Diabetes mellitus | No | 201/517 343 | 126/517 416 | 9.6 | 6.0 | 0.62 (0.49–0.77) | 0.161 |
| | Yes | 40/36 729 | 31/36 656 | 22.3 | 16.5 | 0.73 (0.46–1.17) | |
| Dyslipidaemia | No | 210/527 324 | 146/527 420 | 9.8 | 6.7 | 0.68 (0.55–0.84) | 0.002 |
| | Yes | 31/26 748 | 11/26 652 | 25.0 | 8.7 | 0.35 (0.17–0.69) | |
| Chronic kidney disease | No | 234/548 655 | 149/548 853 | 10.4 | 6.6 | 0.62 (0.51–0.77) | 0.924 |
| | Yes | 7/5417 | 8/5219 | 25.4 | 27.4 | 1.07 (0.39–2.97) | |
| Allergic rhinitis | No | 189/476 591 | 134/476 685 | 9.7 | 6.8 | 0.69 (0.56–0.87) | <0.001 |
| | Yes | 52/77 481 | 23/77 387 | 16.4 | 7.1 | 0.43 (0.27–0.71) | |
| Airway disease | No | 208/533 822 | 135/533 867 | 9.6 | 6.1 | 0.64 (0.51–0.79) | 0.077 |
| | Yes | 33/20 250 | 22/20 250 | 35.7 | 22.8 | 0.64 (0.37–1.09) | |
| Connective tissue disease | No | 244/548 925 | 155/549 063 | 10.0 | 6.8 | 0.68 (0.55–0.83) | 0.004 |

**FIGURE 1** a) Cumulative incidence of interstitial lung disease according to prior coronavirus disease 2019 vaccination history. b) Incidence and risk of interstitial lung disease in non-vaccinated *versus* vaccinated subjects. IR: incidence rate; PY: person-year; HR: hazard ratio.

In conclusion, COVID-19 vaccination was associated with reduced risk of ILD at a population level. Our findings suggest that the risk of COVID-19 vaccination-related ILD is not as high as it was initially concerned.

Taehee Kim[1,6], Hyun Lee[2,6], Cho Yun Jeong[3,6], Sang Woo Yeom[3], Bo-Guen Kim[2], Tai Sun Park[2], Dong Won Park[2], Ji-Yong Moon[2], Tae-Hyung Kim[2], Jang Won Sohn[2], Ho Joo Yoon[2], Sang-Heon Kim[2,7] and Jong Seung Kim[3,4,5,7]

[1]Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea. [2]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Republic of Korea. [3]Research Institute of Clinical Medicine of Jeonbuk National University – Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, Republic of Korea. [4]Department of Medical Informatics, Jeonbuk National University Medical School, Jeonju, Republic of Korea. [5]Department of Otorhinolaryngology-Head and Neck Surgery, Jeonbuk National University Medical School, Jeonju, Republic of Korea. [6]T.H. Kim, H. Lee and C.Y. Jeong contributed equally to this work. [7]J.S. Kim and S-H. Kim contributed equally to this work.

Corresponding author: Jong Seung Kim (kjsjdk@gmail.com)

Provenance: Submitted article, peer reviewed.

Author contributions: J.S. Kim and S-H. Kim were responsible for the conception and design of the study. T. Kim, H. Lee, S.W. Yeom, C.Y. Jeong, B-G. Kim, T.S. Park, D.W. Park, J-Y. Moon, T-H. Kim, J.W. Sohn, H.J. Yoon, J.S. Kim and S-H. Kim undertook the analysis and interpretation of the data. T. Kim, H. Lee, J.S. Kim and S-H. Kim drafted the manuscript. All authors made a critical revision of the manuscript. All authors read and approved the final manuscript.

Conflict of interest: All authors have nothing to disclose.

Support statement: This paper was supported by BK21FOUR 21st Century of Medical Science Creative Human Resource Development Center. This research was supported by the fund of the Biomedical Research Institute, Jeonbuk National University Hospital. Funding information for this article has been deposited with the Crossref Funder Registry.

Ethics statement: This study was approved by the Institutional Review Board of Hallym University Kangnam Sacred Heart Hospital (IRB number 2023-03-022).

## References

1 Wiersinga WJ, Rhodes A, Cheng AC, *et al.* Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020; 324: 782–793.
2 Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; 324: 603–605.
3 Zhao Y-M, Shang Y-M, Song W-B, *et al.* Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine* 2020; 25: 100463.
4 Myall KJ, Mukherjee B, Castanheira AM, *et al.* Persistent post-COVID-19 interstitial lung disease. An observational study of corticosteroid treatment. *Ann Am Thorac Soc* 2021; 18: 799–806.
5 Thompson MG, Stenehjem E, Grannis S, *et al.* Effectiveness of Covid-19 vaccines in ambulatory and inpatient care settings. *New Eng J Med* 2021; 385: 1355–1371.
6 Edwards F, Hamilton FW. Impact of covid-19 vaccination on long covid. *BMJ Med* 2023; 2: e000470.
7 Park JY, Kim JH, Lee IJ, *et al.* COVID-19 vaccine-related interstitial lung disease: a case study. *Thorax* 2022; 77: 102–104.
8 So C, Izumi S, Ishida A, *et al.* COVID-19 mRNA vaccine-related interstitial lung disease: two case reports and literature review. *Respirol Case Rep* 2022; 10: e0938.
9 Yoshifuji A, Ishioka K, Masuzawa Y, *et al.* COVID-19 vaccine induced interstitial lung disease. *J Infect Chemother* 2022; 28: 95–98.
10 Yoo H, Kim SY, Park MS, *et al.* COVID-19 vaccine-associated pneumonitis in the Republic of Korea: a nationwide multicenter survey study. *J Korean Med Sci* 2023; 38: e106.
11 Lee H, Choi H, Yang B, *et al.* Interstitial lung disease increases susceptibility to and severity of COVID-19. *Eur Respir J* 2021; 58: 2004125.

12 Sadarangani M, Marchant A, Kollmann TR. Immunological mechanisms of vaccine-induced protection against COVID-19 in humans. *Nat Rev Immunol* 2021; 21: 475–484.
13 Mohammed I, Nauman A, Paul P, *et al.* The efficacy and effectiveness of the COVID-19 vaccines in reducing infection, severity, hospitalization, and mortality: a systematic review. *Hum Vaccin Immunother* 2022; 18: 2027160.
14 Jia Q, Bielefeldt-Ohmann H, Maison RM, *et al.* Oral administration of universal bacterium-vectored nucleocapsid-expressing COVID-19 vaccine is efficacious in hamsters. *Microbiol Spectr* 2023; 11: e0503522.