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Interstitial lung disease following COVID-19 vaccination: a disproportionality analysis using the Global Scale Pharmacovigilance Database (VigiBase)

Min-Taek Lee,[1,2] Ju Won Lee,[1,2] Hyeon Ji Lee,[1,2] Jong-Min Lee,[1,2] Jae Chol Choi,[3,4] Kang-Mo Gu,[4,5] Sun-Young Jung [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Sun-Young Jung;
jsyoung@cau.ac.kr

ABSTRACT

Background and objective Despite several case reports, population-based studies on interstitial lung disease (ILD) following COVID-19 vaccination are lacking. Given the unprecedented safety issue of COVID-19 vaccination, it is important to assess the worldwide patterns of ILD following COVID-19 vaccination. This study aimed to investigate the signals of COVID-19 vaccine-associated ILD compared with other vaccinations using disproportionality analysis.

Methods We analysed the VigiBase database during the period between 13 December 2020 and 26 January 2023. We adopted the case/non-case approach to assess the disproportionality signal of ILD for COVID-19 vaccines via 1:10 matching by age and sex. We compared COVID-19 vaccines with all other vaccines as the reference group.

Results Among 1 233 969 vaccine-related reports, 679 were reported for ILD. The majority of ILD cases were related to tozinameran (376 reports, 55.4%), Vaxzevria (129 reports, 19.0%) and elasomeran (78 reports, 11.5%). The reporting OR of ILD following COVID-19 vaccination was 0.86 (95% CI 0.64 to 1.15) compared with all other vaccines.

Conclusion No significant signal of disproportionate reporting of ILD was observed for COVID-19 vaccines compared with all other vaccines. Moreover, when compared with the influenza vaccines that are known to cause ILD, no signal was observed. This study results might help decision-making on the subsequent COVID-19 vaccination strategy of ILD. Further large and prospective studies are required for more conclusive evidence.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Since the first case report of interstitial lung disease (ILD) following COVID-19 vaccination was published on 9 June 2021, several ILD cases have been reported. However, population-based studies on ILD following COVID-19 vaccination are lacking.

WHAT THIS STUDY ADDS

⇒ No significant signal of disproportionate reporting of ILD was observed for COVID-19 vaccines compared with other vaccines (reporting OR 0.86, 95% CI 0.64 to 1.15). These findings were consistent across several analyses conducted after considering potential biases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study may provide information that can be useful for making decisions on subsequence COVID-19 vaccine strategies. Moreover, further studies using patient-level information such as disease history and diagnostic test results are required for more conclusive evidence.

INTRODUCTION

As of September 2023, a total of 13.5 billion doses of COVID-19 vaccines have been administered, which averted millions of death worldwide.[1 2] The World Health Organization (WHO) has recently declared the expiration of COVID-19 public health emergency and revise the long-term COVID-19 disease management strategies.[3] It is expected that the COVID-19 vaccines will be included in the regular immunisation schedule similar to other seasonal influenza vaccines.[4 5] To ensure a successful vaccination programme, safety information is important, especially for concerns that are not fully addressed. WHO encourages countries to perform research on vaccines with respect to unknown critical information.[3]

Since August 2021, cases of interstitial lung disease (ILD) following COVID-19 vaccination have been reported, although the underlying aetiology remained poorly understood. ILD is a heterogeneous group of diseases characterised by progressive inflammation and injury to the interstitium and alveoli.[6 7] The incidence of ILD varies according to age, sex, region and race and the prevalence is

approximately 6.3–76.0 cases per 100 000 people.[8 9] The causes of ILD are not clearly known, but several potential risk factors have been suggested, including systemic autoimmune disease and drug exposure.[7] The incidence and prevalence of drug-induced ILD are not well known; however, approximately 2.5%–5.0% of all prevalent ILD cases are estimated to be drug induced.[10 11] Amiodarone and methotrexate are known to cause drug-induced ILD, and the use of these medications has been reported in over 10% of cases with mortality.[10] According to previous reports, vaccination, especially for influenza, is likely to cause ILD.[12–14] Conversely, there have been some case reports suggesting an association between COVID-19 vaccination and the development and progression of ILD.[15–22] It remains unknown whether COVID-19 vaccination-associated ILD has distinct characteristics compared with the disease induced by other vaccines, such as the influenza vaccine.

Spontaneous reports are a useful source to assess signals of rare but serious adverse events (AEs), including COVID-19 vaccine-induced ILD. Studies suggest a temporary increase in reporting rate after product approval and safety alerts due to safety concerns. Therefore, it is necessary to verify ILD cases as the COVID-19 vaccination rate increases. Given that the unprecedented safety issues of COVID-19 vaccines have been raised, it is important to study the identifying characteristics of ILD following COVID-19 vaccination and investigate factors affecting the risk of ILD or reporting rate. Therefore, this study aimed to assess the disproportionality of reporting of ILD associated with COVID-19 vaccines using the case/non-case approach by analysing the WHO global pharmacovigilance database.

METHODS

Data source

We used VigiBase, the largest global pharmacovigilance database with over 30 million reports of suspected AEs of medicines since 1968.[23] It was developed and maintained by WHO-Uppsala Monitoring Centre (UMC). The WHO-UMC receives individual case safety reports (ICSRs) from over 150 countries participating in the WHO programme for international drug monitoring.[23] VigiBase is composed of several medical and drug classification elements, such as the medical dictionary for regulatory activities (MedDRA) and WHODrug. The AEs analysed in our study were investigated using MedDRA version 26.0 (released March 2023) with preferred terms (PTs) and lowest level terms (LLTs), and drugs were coded using WHODrug Global B3/C3-format 1 March 2023.

Variables

We extracted the ICSRs with vaccines as suspected drugs between 13 December 2020 and 26 January 2023.[24] ILD was defined using MedDRA-standardised MedDRA queries (SMQ) (SMQ code=20000042) narrow terms to provide a clear definition and to account for specificity (cases highly likely to be of interest). There were 79 PTs and 132 LLTs in the ILD defined by MedDRA SMQ (online supplemental table 1). The COVID-19 vaccines tozinameran, elasomeran, Vaxzevria, Ad26.COV2.S, Gam-COVID-Vac, NVX-CoV2373 and GBP510 were included in our study and were defined using drug record numbers in WHODrug (online supplemental table 2) and the Anatomical Therapeutic Chemical (ATC) classification (J07BN). The other vaccines were classified according to ATC classification (J07; vaccines). We included physicians, pharmacists and other health professionals as notifier types, and excluded reports with missing values, including age and sex. The dates on which the reports were entered into the VigiBase were arranged by quarters. The geographical regions were divided into five groups: Africa, the Americas, South-East Asia, Europe, Eastern Mediterranean and Western Pacific. Using ICSRs, we calculated the time-to-onset, which is the time interval between vaccine administration and initiation of the event. In VigiBase, ICSRs contain multiple AEs with several different time-to-onset. Therefore, we selected the vaccine-AE pairs with the most information, including dechallenge action/outcome and rechallenge action/outcome as representatives. Moreover, if vaccine–AE pairs have an equal number of outcome information, we chose the ICSR with the shortest time-to-onset. Furthermore, we regarded time-to-onset as an outlier by individual pairs (coded as missing values) if it was outside the study period.

Statistical analysis

We performed a descriptive analysis of ILD cases and non-cases. Continuous variables, including time-to-onset, were presented as the mean±SD and were compared using the Student's t-test. The categorical variables, including reported quarter, age groups, sex, type of report, type of COVID-19 vaccines, seriousness, region and type of notifier, were reported as numbers (percentage) and compared using the χ^2 test and Fisher's exact test.

The association between COVID-19 vaccines and ILD was evaluated using case/non-case analysis.[25] The case/non-case analysis is a disproportionality approach performed in the pharmacovigilance databases developed during the early 1980s.[26] Briefly, it is similar to case–control analysis but uses non-case instead of control. In the spontaneous AE report database, the ICSRs indicate reports of exposure to the drug of interest at least once and any AE experienced any AE at least once.[25] In our study, cases were defined as ICSRs of ILD while the remaining ICSRs were considered non-cases. The primary analysis compared the COVID-19 vaccines with all other vaccines. We compared ILD cases and non-cases by 1:10 matching according to age and sex as matching variables. The logistic regression model was used for calculating reporting ORs (RORs) and 95% CI.[27] We determined the detection of a signal according to the three criteria: the

ROR is greater than 1, the lower bound 95% CI is greater than 1 and the number of cases is greater than 3.[25]

We performed subgroup analyses using stratification by age groups, sex and region. We determined factors reported in previous case reports that may affect the occurrence of ILD. Individuals were categorised into two groups based on (1) age (<65 and ≥ 65 years), (2) sex (male and female) and (3) region (Western Pacific region and the other regions).

Moreover, sensitivity analyses were performed to identify diverse AE definitions and the extent of contribution of potential biases as follows. First, we designed sensitivity analysis 1 to define ICSRs with vaccines as suspected, concomitant and interaction drugs, as opposed to the primary analysis performed with suspected drugs. Second, we defined ILD using both MedDRA SMQ narrow and broad terms (broad search), thereby including all possible cases. Third, we excluded ICSRs that included drugs known to cause ILD, such as those used to treat cancer, rheumatic diseases, infection and cardiac diseases (online supplemental table 2) as these can influence the likelihood of detecting a signal between COVID-19 vaccines (drug competition bias).[28] Fourth, since events known as scientific and specific medical concerns about COVID-19 vaccines could affect other signal events (competition bias), we excluded reports containing 14 AEs of special interest of COVID-19 vaccine, including myocarditis, pericarditis and thrombosis, as suggested by Brighton collaboration.[29] Fifth, ICSRs reported as serious AEs were restricted in sensitivity analysis 5. The Weber effect could arise due to the market authorisation of new COVID-19 vaccines. Sixth, we included ICSRs with a reporting date before 9 August 2021, which may have influenced reporting in sensitivity analysis 6 (notoriety bias).[15] Finally, in sensitivity analysis 7, we compared the COVID-19 vaccines with the influenza vaccines (ATC: J07BB, influenza vaccines) as a positive control. This choice was based on previous reports[12–14] indicating that influenza vaccines have been known to cause ILD. Additionally, there is a report suggesting that the mechanism of ILD following COVID-19 vaccination may be similar to the mechanism of ILD following influenza vaccination.[13] We have organised the overall analysis strategies in online supplemental table 3.

Patient and public involvement

As this is a secondary database study, the database is anonymised and served without identifiers of the study participants. The patients were not involved in the design, conduct or dissemination of this study.

RESULTS

A total of 1 233 969 reports with AEs following COVID-19 vaccination were identified from 12 December 2020 to 26 January 2023. After 1:10 matching by age group and sex, 7469 reports were determined to be ILD cases (679 ICSRs) and non-cases (6790 ICSRs) (figure 1). The

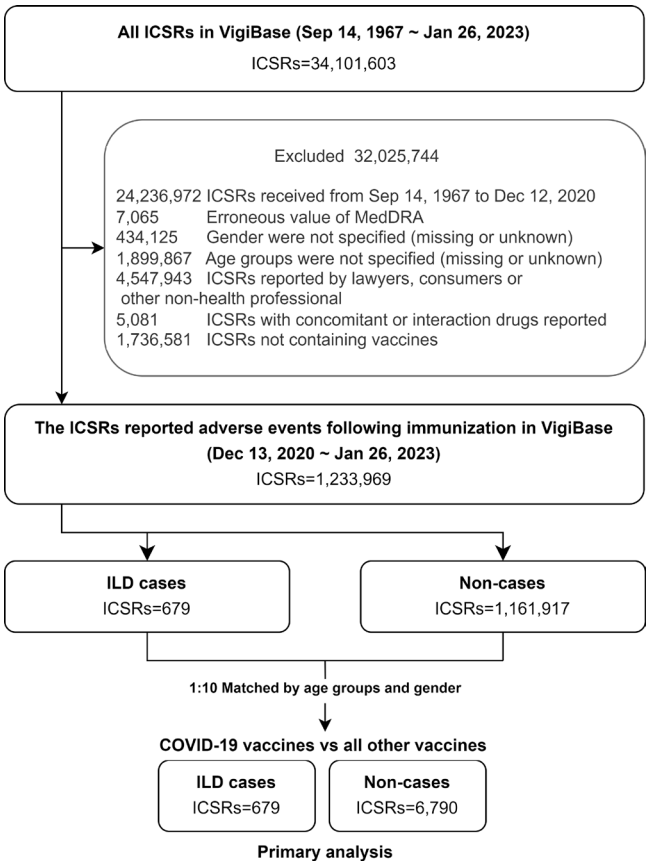

Figure 1 Flow chart of primary analysis. Primary analysis compared COVID-19 vaccines with all other vaccines. ICSR, individual case safety report; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities.

characteristics of ILD cases/non-cases of the primary analysis, including reported quarter, age groups, sex, type of report, type of vacines, seriousness, region and time-to-onset, are shown in table 1. This study analysed six COVID-19 vaccines, including tozinameran, elasomeran, Vaxzevria, Ad26.COV2.S., Gam-COVID-Vac and NVX-CoV2373. GBP510 was not included in our study. Most of the reports were received in the third quarter of 2021 (104 ICSRs, 17.1%) with ILD cases following COVID-19 vaccination being first reported (table 1). A significant proportion of ILD cases received tozinameran (376 ICSRs, 55.4%) and were Europeans (577 reports, 85.0%). Serious AEs including death, life-threatening conditions and hospitalisation/prolonged hospitalisation were more likely in ILD cases (625 ICSRs, 92.1%) compared with non-cases (2343 ICSRs, 34.5%). ILD cases had the highest proportion of reports received by physicians (527 ICSR, 77.6%), followed by other health professionals (102 ICSRs, 105.8%) and pharmacists (50 ICSRs, 7.4%). The median time-to-onset was 7 (IQR 1–36) days for ILD cases and 1 (IQR 0–15) day for non-cases (p=0.0077).

The number of monthly ILD cases following COVID-19 vaccination is shown in figure 2. Most of the cases of ILD following COVID-19 vaccination (40 cases) were

Table 1 Characteristics of interstitial lung disease (ILD) and non-ILD cases from VigiBase database: primary analysis (compared COVID-19 vaccines with all other vaccines)

	ILD cases (N=679)	Non-cases (N=6790)	
	N (%)	N (%)	P value
Reported quarter (Q)			0.036
2020.4Q (13 December 2020–31 December 2020)	0 (0.0)	19 (0.3)	
2021.1Q (1 January 2021–31 March 2021)	49 (7.2)	703 (10.4)	
2021.2Q (1 April 2021–30 June 2021)	104 (15.3)	1193 (17.6)	
2021.3Q (1 July 2021–30 September 2021)	116 (17.1)	1066 (15.7)	
2021.4Q (1 October 2021–31 December 2021)	104 (15.3)	1002 (14.8)	
2022.1Q (1 January 2022–31 March 2022	102 (15.0)	883 (13.0)	
2022.2Q (1 April 2022–30 June 2022)	80 (11.8)	820 (12.1)	
2022.3Q (1 July 2022–30 September 2022)	44 (6.5)	463 (6.8)	
2022.4Q (1 October 2022–31 December 2022)	66 (9.7)	560 (8.3)	
2023.1Q (1 January 2023–26 January 2023)	14 (2.1)	81 (1.2)	
Age groups			1
0–27 days	2 (0.3)	20 (0.3)	
28 days to 23 months	26 (3.8)	260 (3.8)	
2–11 years	4 (0.6)	40 (0.6)	
12–17 years	4 (0.6)	40 (0.6)	
18–44 years	92 (13.6)	920 (13.6)	
45–64 years	187 (27.5)	1870 (27.5)	
65–74 years	144 (21.2)	1440 (21.2)	
≥75 years	220 (32.4)	2200 (32.4)	
Sex			1
Male	356 (52.4)	3560 (52.4)	
Female	323 (47.6)	3230 (47.6)	
Report type			<0.0001
Spontaneous	618 (91.0)	6205 (91.4)	
Report from study	54 (8.0)	317 (4.7)	
Other	7 (1.0)	267 (3.9)	
Not available to sender (unknown)	0 (0.0)	1 (0.0)	
Vaccines type			
COVID-19 vaccines	626 (92.2)	6331 (93.2)	0.3039
Tozinameran	376 (55.4)	3324 (49.0)	0.0014
Elasomeran	78 (11.5)	642 (9.5)	0.0871
Vaxzevria	129 (19.0)	1492 (22.0)	0.073
Ad26.COV2.S	8 (1.2)	224 (3.3)	0.0024
Gam-COVID-Vac	0 (0.0)	2 (0.0)	0.6547
NVX-CoV2373	0 (0.0)	3 (0.0)	1.000
Influenza vaccines	34 (5.0)	123 (1.8)	<0.0001
Pneumococcal vaccines	11 (1.6)	105 (1.6)	0.8824
Drug known to cause ILD included in the ICSRs*			
Cancer therapy	17 (2.5)	10 (0.2)	<0.0001
Rheumatology therapy	27 (4.0)	25 (0.4)	<0.0001
Anti-infection agent	3 (0.4)	3 (0.0)	0.0121
Cardiology drugs	62 (9.1)	241 (3.6)	<0.0001

Continued

Table 1 Continued

	ILD cases (N=679)	Non-cases (N=6790)	
	N (%)	N (%)	P value
Serious			<0.0001
Yes	625 (92.1)	2323 (34.5)	
Seriousness			<0.0001
Death	116 (17.1)	287 (4.2)	
Life threatening	97 (14.3)	162 (2.4)	
Caused/Prolonged hospitalisation	285 (42.0)	582 (8.6)	
Disabling/incapacitating	13 (1.9)	91 (1.3)	
Congenital anomaly/birth defect	0 (0.0)	3 (0.0)	
Other	114 (16.8)	1218 (17.9)	
Region			<0.0001
African	4 (0.6)	364 (5.4)	
Americas	54 (8.0)	632 (9.3)	
South-East Asia	6 (0.9)	121 (1.8)	
European	577 (85.0)	4398 (64.8)	
Eastern Mediterranean	8 (1.2)	342 (5.0)	
Western Pacific	30 (4.4)	933 (13.7)	
Notifier type			<0.0001
Physician	527 (77.6)	3675 (54.1)	
Pharmacist	50 (7.4)	1055 (15.5)	
Other health professional	102 (15.0)	2060 (30.3)	
Time to onset (case=574, non-case=6064)			0.0077
Mean±SD	32.7±64.7	26.6±57.3	
Median (Q1–Q3)	7 (1–35)	1 (0–15)	

*Cancer therapy: bleomycin; gemcitabine; epidermal growth factor receptor-targeted agent (erlotinib, gefitinib, panitumumab, cetuximab); mammalian target of rapamycin-inhibitor (everolimus, temsirolimus, sirolimus); immune checkpoint inhibitor (nivolumab, pembrolizumab, avelumab, durvalumab, ipilimumab), rheumatology drugs: methotrexate; leflunomide, biological disease-modifying anti-rheumatic drugs (tumour necrosis factor) agent (infliximab, etanercept, adalimumab), tocilizumab, rituximab), anti-infection agents (nitrofurantoin, daptomycin, interferon), cardiology drugs (amiodarone, bepridil, statin (lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, rosuvastatin, cerivastatin)).
ICSRs, individual case safety reports.

reported in September 2021, while the first report was from January 2021. The number of reports decreased steadily until the end of the study. Serious AE reports accounted for 84.4% to 100% of all ILD cases following COVID-19 vaccination (figure 2).

We identified characteristics of ILD cases by COVID-19 vaccines, influenza vaccines and other vaccines. The COVID-19 vaccines contained reports from European and had the longest median time-to-onset (1 (IQR 1–36) day) than the influenza vaccine (5 (IQR 2–23)) and others (6 (IQR 1–21)) (online supplemental table 4). The most frequently reported AEs with regard to PT or LLT were pneumonitis (134 ICSRs, 19.7%), ILD (70 ICSRs, 10.3%) and interstitial pneumonia (46 ICSRs, 6.8%) in ILD cases (online supplemental table 5). AEs that included both narrow and broad terms were aligned with the AEs from narrow terms. Details of ILD cases are provided in online supplemental tables 4 and 5.

Case/non-case analysis

The results of ILD cases/non-cases, including those of primary, secondary and subgroup analyses, are shown in table 2. The ROR of ILD following COVID-19 vaccination was 0.86 (95% CI 0.64 to 1.15) compared with other vaccines. The ROR of mRNA vaccines was 0.99 (95% CI 0.73 to 1.34), tozinameran was 0.98 (95% CI 0.73 to 1.33) and elasomeran was 1.04 (95% CI 0.71 to 1.50). Moreover, no signal of disproportionate reporting was observed in viral vector COVID-19 vaccines (viral vector COVID-19 vaccines ROR 0.69 (95% CI 0.50 to 0.96); Vaxzevria ROR 0.75 (95% CI 0.53 to 1.05) and Ad26.COV2.S ROR 0.32 (95% CI 0.15 to 0.67)) (table 2).

In the subgroup analysis of primary analysis, we did not find an increased reporting of ILD according to age groups, sex and region (table 3, online supplemental table 6). The ILD following COVID-19 vaccination was not associated with a disproportionality signal regardless

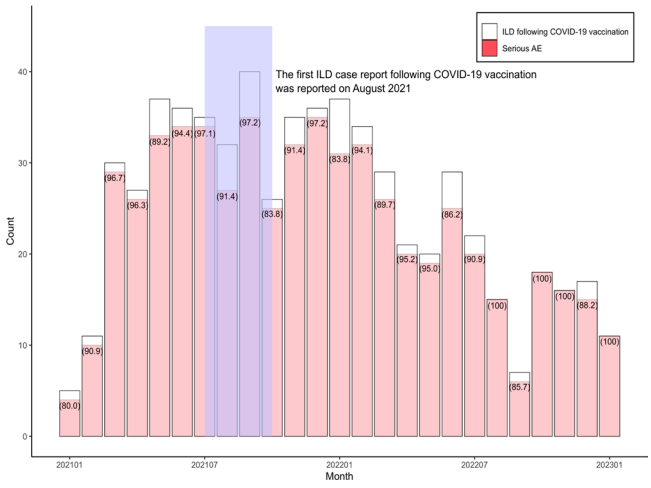

Figure 2 The number of ILD cases following COVID-19 vaccination during the study period. The brackets () present the proportion of serious AE among ICSRs reported ILD following COVID-19 vaccination. AE, adverse event; ICSR, individual case safety report; ILD, interstitial lung disease.

of age groups (under 65 years; ROR 0.94 (95% CI 0.65 to 1.35), 65 years and older; ROR 0.70 (95% CI 0.41 to 1.17). The COVID-19 vaccination emerged with no signal in both males and females (males ROR 0.81 (95% CI 0.55 to 1.19), females ROR 0.93 (95% CI 0.59 to 1.46)). There was no signal when stratifying Western Pacific region and the other regions (ROR 0.42 (95% CI 0.16 to 1.14) and ROR 0.88 (95% CI 0.65 to 1.21).

The results of the sensitivity analyses were similar to those of the primary analysis (figure 3, online supplemental table 7). There was no disproportionality signal when considering diverse AE definitions and potential biases (figure 3, online supplemental table 7). The ROR of influenza vaccines was 0.44 (95% CI 0.27 to 0.71). The results of sensitivity analysis 7 compared with influenza vaccines were consistent with the primary analysis (online supplemental tables 8 and 9)

DISCUSSION

The present study aimed to identify the characteristics of ILD following COVID-19 vaccination and the disproportionality between COVID-19 vaccines and ILD using the global pharmacovigilance database. We identified 679 ILD cases from VigiBase defined using MedDRA SMQ and performed disproportionality analysis. To the best of our knowledge, this is the first study to investigate the signals of disproportionate reporting of ILD associated with COVID-19 vaccines. Compared with other vaccines, no significant signal of disproportional reporting of ILD was observed for COVID-19 vaccines. These findings were consistent across several analyses conducted after considering potential biases. Moreover, the signal of disproportionality was not detected when compared with the influenza vaccine which is known to induce ILD.

In our study, reports received from European accounted for the majority of ILD cases (85.0%) following COVID-19 vaccination. In contrast to the present study, most ILD cases following COVID-19 vaccination have been reported in South-East Asia, including South Korea and Japan since Park *et al* reported the first ILD case following mRNA COVID-19 vaccination.[15 16 18–20] Kono *et al* suggested that South-East Asian population should be carefully monitored since it is at a high risk of COVID-19 vaccine-related ILD.[30] Among 30 cases of ILD identified following COVID-19 vaccination in the Western Pacific, which is classified as Asia by WHO, and the signal of ILD was not detected when compared with other vaccines (ROR 1.68, 95% CI 0.68 to 4.16) (table 2). However, the result of subgroup analysis according to the region should be interpreted with caution because of the small number of cases and incomplete information on ICSRs.

Table 2 Reporting OR (ROR) of COVID-19 vaccines and all other vaccines (primary analysis)

Type of analysis	ILD cases	Non-cases	ROR (95% CI)
Primary analysis (cases: 679, non-cases: 6790)			
The other vaccines	53 (7.8)	459 (6.8)	Reference
COVID-19 vaccines	626 (92.2)	6331 (93.2)	0.86 (0.64 to 1.15)
mRNA COVID-19 vaccines	448 (66.0)	3912 (57.6)	0.99 (0.73 to 1.34)
Tozinameran	373 (58.9)	3282 (54.4)	0.98 (0.73 to 1.33)
Elasomeran	73 (11.5)	611 (10.1)	1.04 (0.71 to 1.50)
Viral vector COVID-19 vaccines	137 (20.2)	1718 (25.3)	0.69 (0.50 to 0.96)
Vaxzevria	126 (19.9)	1461 (24.2)	0.75 (0.53 to 1.05)
Gam-COVID-Vac	0 (0.0)	2 (0.0)	NC
Ad26.COV2.S	8 (1.3)	220 (3.6)	0.32 (0.15 to 0.67)
Protein-based COVID-19 vaccines	0 (0.0)	3 (0.0)	NC
NVX-CoV2373	0 (0.0)	3 (0.1)	NC
Others	41 (6.0)	698 (10.3)	0.51 (0.33 to 0.78)

ILD, interstitial lung disease; NC, not calculated.

Table 3 Reporting OR (ROR) of COVID-19 vaccines and all other vaccines in subgroup analysis

Type of analysis	ILD cases	Non-cases	ROR (95% CI)
Subgroup analysis			
Age			
Age <65 (case=315, non-case=3150)			
The other vaccines	36 (11.4)	339 (10.8)	Reference
COVID-19 vaccines	268 (85.1)	2447 (77.7)	0.94 (0.65 to 1.35)
Age ≥65 (case=364, non-case=3640)			
The other vaccines	17 (4.7)	120 (3.3)	Reference
COVID-19 vaccines	347 (95.3)	3520 (96.7)	0.70 (0.41 to 1.17)
Gender			
Male (case=356, non-case=3560)			
The other vaccines	31 (8.7)	254 (7.1)	Reference
COVID-19 vaccines	325 (91.3)	3306 (92.9)	0.81 (0.55 to 1.19)
Female (case=323, non-case=3230)			
The other vaccines	22 (6.8)	205 (6.4)	Reference
COVID-19 vaccines	301 (93.2)	3025 (93.7)	0.93 (0.59 to 1.46)
Region			
Western Pacific region (case=30, non-case=933)			
The other vaccines	5 (16.7)	73 (7.8)	Reference
COVID-19 vaccines	25 (83.3)	860 (92.2)	0.42 (0.16 to 1.14)
The other regions (case=649, non-case=5857)			
The other vaccines	48 (7.4)	386 (6.6)	Reference
COVID-19 vaccines	601 (92.6)	5471 (93.4)	0.88 (0.65 to 1.21)

ILD, interstitial lung disease.

A previous systematic review of drug-induced ILD identified male has been as a risk factor for drug-induced ILD, especially in those treated with amiodarone, methotrexate, epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) and premetrexed.[31] Males were predominant in previous case reports of ILD related to COVID-19 vaccination.[15 16 18–20] However, this study observed no signal of disproportionate reporting regardless of sex (males (ROR 0.81, 95% CI 0.55 to 1.19), females (ROR 0.93, 95% CI, 0.59 to 1.46)) (online supplemental table 6). Further studies are required to identify the risk according to demographic characteristics.

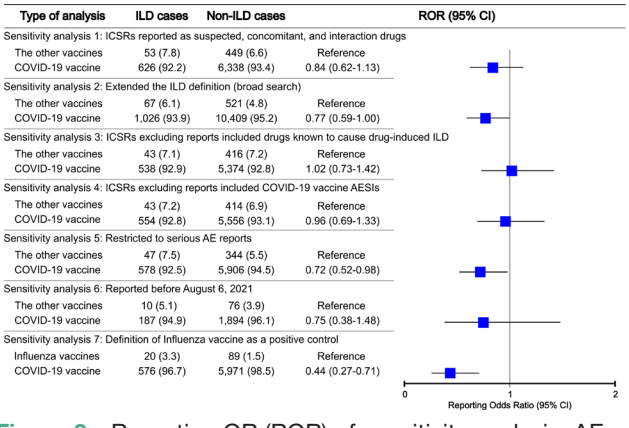

Figure 3 Reporting OR (ROR) of sensitivity analysis. AE, adverse event; AESI, adverse event of special event; ICSR, individual case safety report; ILD, interstitial lung disease; MedDRA, medical dictionary for regulatory activities; SMQ, standardised MedDRA queries.

We analysed the data of spontaneous reporting systems to assess signals of AE of COVID-19 vaccination. The spontaneous reporting systems have several biases due to factors that could affect reporting, which results in incorrect signal detection. These biases can be notoriety bias, information bias, selection bias and competition bias.[25 32 33] We implemented different minimisation strategies against these biases. First, we designed a primary analysis to address factors that could lead to information bias by considering to be suspected, healthcare professionals and complete information on age groups and sex. Moreover, in sensitivity analysis 2, we used MedDRA SMQ with narrow and broad terms. This result was in line with the primary analysis that showed no signal of disproportionate reporting (ROR 0.77, 95% CI 0.59 to 1.00). Second, for competition bias, it is necessary to eliminate factors associated with vaccines/AEs of interest (sensitivity analyses 3, 4). Results derived from sensitivity analysis considering competition biases showed that

COVID-19 vaccines had no disproportionality signal of ILD compared with the other vaccines (ROR 1.02, 95% CI 0.73 to 1.42 and ROR 0.96, 95% CI, 0.69 to 1.33, respectively). Third, in pharmacovigilance, temporal bias (the Weber effect or notoriety bias) refers to variation in the number of reports after a specific event, such as safety alerts and market authorisation. The signal of ILD was not observed when minimising temporal biases; the RORs of sensitivity analyses 5 and 6 were 0.72 (95% CI 0.52 to 0.98) and 0.75 (95% CI 0.38 to 1.48), respectively. Fourth, we defined reference groups that received influenza and other vaccines instead of all other drugs to avoid selection bias. The analysis using influenza vaccines as a positive control in the secondary analysis showed that COVID-19 vaccines emerged with no signal when compared with influenza vaccines (ROR 0.44, 95% CI 0.27 to 0.71). However, the risk–benefits of COVID-19 vaccines should be carefully assessed.

The mechanisms of COVID-19 vaccine-induced ILD are unclear. To date, both cytotoxicity and immune-mediated lung injury are considered as main mechanisms that initiate drug-induced ILD. Although it is rare, the event can be fatal and patients might require hospitalisation.[34] According to previous reports, the influenza vaccination can induce ILD by increasing the levels of inflammatory cytokines.[12] Several cases of COVID-19 mRNA vaccine associated ILD have been reported.[15–21] Given the similar clinical characteristics with influenza vaccine-induced ILD, including onset time, chest CT findings and responsiveness to corticosteroids, it can be speculated that ILD following COVID-19 vaccination might also be due to immune-mediated pulmonary injury. These studies suggest that COVID-19 vaccination induces immune-mediated injury to the lungs through T-cells, which adopt a predominant type one phenotype in susceptible patients.[17–21 35] However, further studies with a large number of ILD patients who received the COVID-19 vaccines are needed.[12 15]

This study has several limitations. First, selective reporting of AEs might have been compromised in the spontaneous reporting database although we strived to minimise biases. During the pandemic, the number of ICSRs following COVID-19 vaccination increased rapidly, which might have resulted in differential reporting rates and influenced parameters. We applied 1:10 exact matching to reduce the imbalance between case and non-case and performed various analyses. The results of our study did not provide exhaustivity of COVID-19 vaccine-induced ILD although it suggests focusing on the risk. Second, we analysed ICSRs without causality assessment. However, VigiBase contains essential information required for causality assessment, including age, sex, primary reporter and time-to-onset. Third, concerns on the validity of ILD in spontaneous reporting database might be raised. To overcome this limitation, we restricted physicians (77.6%), pharmacists (7.4%) and other health professionals (14.8%) as notifier types and defined ILD using MedDRA SMQs, which are validated by expert discussion. Fourth, in the present study, the majority of ILD cases following vaccination were predominantly in the European population, which may introduce bias due to population heterogeneity. Fifth, previous studies have suggested that COVID-19 infection can lead to the occurrence or exacerbation of ILD, referred to as post-COVID-19 ILD. Notably, the VigiBase we used cannot ascertain the COVID-19 infection status. Therefore, the study findings should be interpreted with caution. Finally, this study did not assess the risk of specific molecular components of vaccines. The excipients such as adjuvants, stabilisers, preservatives and trace components can cause AE following immunisation. Therefore, besides vaccines, the safety of excipients should also be evaluated. Despite these limitations, our study used a global pharmacovigilance database with over 30 million ICSRs and could offer additional hypotheses for AEs. In addition, the case/non-case approach allowed us to study rare AEs and could represent the use of drugs in real world settings.[25] Since there were no population-based studies and previous case reports have included exacerbation of pre-existing ILD with death, additional safety studies are needed.

CONCLUSION

In conclusion, we identified no significant disproportionality signal of ILD associated with COVID-19 vaccines using global pharmacovigilance database. This finding is consistent regardless of the subpopulation. Furthermore, the disproportional analysis compared with the influenza vaccines that are known to cause ILD emerged with no signal. However, serious AE accounted for the majority of ILD cases following COVID-19 vaccination and events, including hospitalisations, have been reported. We suggest careful monitoring of COVID-19 vaccine-induced ILD. This study may provide information that can be useful for making decisions on subsequence COVID-19 vaccine strategies. However, further studies using patient-level information such as disease history and diagnostic test results are required for more conclusive evidence.

Author affiliations
[1]College of Pharmacy, Chung-Ang University, Seoul, Korea
[2]Department of Global Innovative Drugs, The Graduate School of Chung-Ang University, Seoul, Korea
[3]Division of Pulmonary and Allergy Medicine, Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong-si, Gyeonggi-do, Korea
[4]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, South Korea
[5]Division of Pulmonary and Allergy Medicine, Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Korea

Contributors M-TL and S-YJ participated in the conception and design of study. M-TL and S-YJ participated in the data acquisition and data analysis. M-TL, JWL, JCC, K-MG and S-YJ participated in the data interpretation. M-TL participated in the draft of the manuscript. JWL, HJL, J-ML, JCC and K-MG helped to revise the manuscript for intellectual content. All authors read and approved the final manuscript. S-YJ is reponsible for the overall content as guarantor.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved for exemption from review by the Institutional Review Board of Chung-Ang University (IRB number: 1041078-201903-HR-071-01), because this study analyaed a secondary database. Informed consent from subjects was waived due to the database containing anonymised data that cannot identify study subjects.

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ORCID iD

Sun-Young Jung http://orcid.org/0000-0003-2032-112X

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