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RESEARCH

Autoimmune disorders reported following COVID-19 vaccination: A disproportionality analysis using the WHO database

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Abstract

Purpose Owing to adverse event following immunization (AEFI) related to autoimmune disorders and coronavirus disease 2019 (COVID-19) vaccines sharing common biological mechanisms, identifying the risk of AEFIs associated with COVID-19 vaccines remains a critical unmet need. We aimed to assess the potential safety signals for 16 AEFIs and explore co-reported adverse events (AEs) and drugs using the global database of the World Health Organization, VigiBase.

Methods We assessed the occurrence of 16 AEFIs following COVID-19 vaccination through the Standardized MedDRA Queries group "Immune-mediated/Autoimmune Disorders" from MedDRA and performed a disproportionality analysis using reporting odds ratio (ROR) and information component (IC) with 95% confidence intervals (CIs).

Results We identified 25,219 events associated with COVID-19 vaccines in VigiBase. Although rare, we detected four potential safety signals related to autoimmune disorders following COVID-19 vaccination, including ankylosing spondylitis or psoriatic arthritis (ROR 1.86; 95% CI 1.53–2.27), inflammatory bowel disease (ROR 1.77; 95% CI 1.60–1.96), polymyalgia rheumatica (ROR 1.42; 95% CI 1.30–1.55), and thyroiditis (ROR 1.40; 95% CI 1.30–1.50), with positive IC_{025} values. The top co-reported AEs were musculoskeletal disorders, and immunosuppressants were the most representative co-reported drugs.

Conclusion In addressing the imperative to comprehend AEFI related to autoimmune disorders following COVID-19 vaccination, our study identified four potential safety signals. Thus, our research underscores the importance of proactive safety monitoring for the identification of the four AEFIs following COVID-19 vaccination, considering the associated advantages.

Keywords Autoimmune disorders · Coronavirus disease (COVID-19) vaccines · Adverse events · Reporting odds ratio · Pharmacovigilance

Introduction

Adverse event following immunization (AEFI) related to autoimmune disorders can occur to various degrees and arise due to the loss of self-antigen tolerance [1]. As coronavirus disease 2019 (COVID-19) vaccines share common biological mechanisms with AEFIs [2], identifying the risk of AEFIs associated with COVID-19 vaccines remains a critical unmet need. Vaccine-induced immunomodulation can increase the synthesis of type 1 interferons, which are linked to the pathogenesis of AEFIs. Although clinical trials have not reported serious safety concerns, including AEFIs related to autoimmune disorders [3], safety concerns regarding AEFIs following COVID-19 vaccination during large-scale vaccination programs have been raised [4–7].

Several prior studies have reported the risk of AEFIs from COVID-19 vaccines. Emerging evidence has revealed that autoimmune rheumatic diseases and hepatitis can

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occur following COVID-19 vaccination [8, 9]. A prospective cohort study suggested an association between vaccine-induced immune thrombotic thrombocytopenia and the virus-vector-based vaccines such as ChAdOx1 nCoV-19 and Ad26.CoV2.S vaccines [10]. These events resulted in a suspension of the utilization of the ChAdOx1 nCoV-19 vaccine across multiple European countries, with Denmark subsequently opting to exclude this entirely from its overall vaccination initiative [11]. Additionally, some cohort studies have suggested disproportionate reporting, indicating an increased risk of Guillain-Barré syndrome associated with Ad26.COV2.S vaccination [12, 13]. In response, regulatory agencies have requested that monitoring AEFIs triggered by COVID-19 vaccination be strengthened [14]. As autoimmune safety events are expressed in various forms, signal detection across a broad AEFI range is highly encouraged. Despite co-reported adverse events (AE) and potential concomitant drug interactions that may provide clinically important evidence to confirm the safety profile of COVID-19 vaccines, limited evidence is available regarding co-reported AEs and drugs related to AEFIs from COVID-19 vaccines.

Our primary objective was to assess the potential safety signals of 16 AEFIs using retrospective disproportionality analysis. The secondary objective was to explore the co-reported AEs and drugs to provide additional evidence of the safety profile of COVID-19 vaccines using the global database of the World Health Organization (WHO) VigiBase.

Methods

Data source

In this study, we utilized information sourced from VigiBase, renowned as the preeminent pharmacovigilance database globally. The database is under the management of the Uppsala Monitoring Centre, which serves as the WHO Collaborating Centre for International Drug Monitoring. VigiBase has contained approximately 30 million Individual Case Safety Reports (ICSR) from 153 member countries. Post-marketing data were sent to VigiBase, suggesting that a certain drug may be linked to suspected adverse drug reactions [15]. Specifically, VigiBase gathers all ICSRs relevant to drugs or vaccines, all of which have been spontaneously reported from various sources in a structured form. The abstracted data include patient demographics (age at AE occurrence, sex, region, qualification of the reporter, and date of reporting) and clinical characteristics (suspect/interacting and concomitant drugs, reported reaction with severity, therapeutic indication, outcome recovery level, and time-to-onset). Reactions are identified and coded through standardized "Medical Dictionary for Regulatory Activities (MedDRA, version 24.1)" classification terms. MedDRA classifies medical terminology at the general level (system organ classes, SOC) and in detailed preferred terms (PTs). Time-to-onset (TTO), defined as the duration from suspected drug initiation to onset AEs, is also determined. To mitigate the influence of the impact of extreme values, we estimated the range of TTO based on the interquartile range (IQR). IQR is the range from the first quartile (Q1) and the third quartile (Q3), with Q1 representing the lowest 25% of the data and Q3 indicating the point below which 75% of the data.

Study design and population

We included spontaneous reports of patients vaccinated against COVID-19 from VigiBase between 11 December 2020 (the first day of the COVID-19 vaccine report in VigiBase) and 26 July 2022. We first identified all AEFIs that occurred in response to the COVID-19 vaccines. In reports of AEFIs associated with COVID-19 vaccines, COVID-19 vaccines were restricted to "suspected" or "interacting" drugs. Reports of AEFIs associated with the COVID-19 vaccines were defined as cases, whereas reports of other AEs were defined as non-cases. We included the following COVID-19 vaccines: (1) BNT162b2/Pfizer (mRNA vaccine platforms), (2) mRNA-1273/Moderna (mRNA vaccine platforms), (3) Ad.26. COV2.S/Johnson & Johnson (viral vectors vaccine platforms), and (4) ChAdOx1 nCoV-19/AstraZeneca (viral vectors vaccine platforms).

Outcome measures

AEFI referred to any unexpected event that occurs after immunization, and it may not necessarily be causally associated with the vaccination. We assessed the occurrence of the following 16 AEFIs related to autoimmune disorders: ankylosing spondylitis or psoriatic arthritis, hemolytic anemia/idiopathic, idiopathic inflammatory myopathies, idiopathic thrombocytopenic purpura (ITP), inflammatory bowel disease (IBD), mixed connective tissue disorder, multiple sclerosis, myasthenia gravis, pernicious anemia, polymyalgia rheumatica, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, thyroiditis, type 1 diabetes, and vasculitis. To select AEFIs related to autoimmune disorders for inclusion in our study, we examined the existing literature, focusing on autoimmune disorders associated with vaccines [16, 17]. Subsequently, we reviewed a list of autoimmune disorders that warrant attention based on clinical features, referencing the Standardized MedDRA Queries (SMQ) group "Immune-mediated/Autoimmune Disorders" from MedDRA (preferred term level). Generally, the SMQ is validated and exhaustive and comprises preferred terms that are consistently classified based on grouping areas of

interest [18]. Following consultation with physicians, we finalized the outcome list based on 16 autoimmune disorders deemed essential for investigating potential associations with COVID-19 vaccines.

Statistical analysis

Descriptive statistics were calculated for the demographic (age, sex, and world region) and clinical (vaccine type, AEFI outcome, co-reported AEs, co-reported drugs, and time to AEFI occurrence) characteristics of each report of interest.

We performed a disproportionality (or case-non-case) analysis to explore the correlation between COVID-19 vaccination and AEFIs. A disproportionality analysis is a comparison between the proportion of undesirable effects reported in a specific group and the proportion in which the same effects are reported in the control group. To ensure comparability, we used the reports of AEFIs from all other vaccines, except the COVID-19 vaccines, as a comparator. These analyses estimate disproportionality in reporting using the reporting odds ratio (ROR) and information component (IC), which serve as indicators of disproportionate reporting. The ROR is an appropriate measure of association and serves as an odds ratio in case-control studies. If the lower boundary of the 95% confidence interval (CI) was greater than 1.00, it suggested that specific AEs were reported more than expected [19]; this can be interpreted as a pharmacovigilance signal. The IC is deemed as a threshold for signal detection, and its calculation is based on a Bayesian neural network developed by the UMC (the Uppsala Monitoring Centre). IC_{025}, which is the 95% lower boundary of IC, was used. A positive IC_{025} value is likely to have implications for the close relationship between a drug and an AEs.

We gathered co-reported AEs following standardized sections classified according to MedDRA "System Organ Classes" (SOCs), comprising clusters of AEs of interest by organs. We also evaluated co-reported AEs associated with AEFIs. Furthermore, co-reported drugs were described to provide descriptive information about potential concomitant drug interactions. We considered co-reported drugs, defined as suspected or interacting medicines, along with COVID-19 vaccines. We categorized the co-reported drugs based on their therapeutic effects and chemical characteristics using the Anatomical Therapeutic Chemical Classification System ATC system, a multi-label classification system managed by the WHO [20].

We also analyzed the TTO of the AEs of interest. Only AEFIs occurring within 28 days of the COVID-19 vaccination were included in the TTO analysis. According to previous studies, AEs occurring after 28 days are deemed unlikely to be associated with vaccination [21].

We conducted a sensitivity analysis by switching the comparator to the influenza vaccine to confirm whether the disproportionate reporting of AEFIs related to COVID-19 vaccines was overrated or underrated. Vaccines possess distinctive attributes compared to other medications, primarily serving preventive purposes, requiring less frequent administration, and targeting a substantial proportion of the population. Consequently, we used the influenza vaccine as an active comparator in our sensitivity analysis. We also performed a sensitivity analysis that removed reports of immunosuppressants as suspected or interacting drugs to reduce the possibility of misclassification. All the analyses were performed using SAS 9.4 version (SAS Inc., Cary, NC, USA).

Results

During the study period, 4,095,997 AEFIs associated with COVID-19 vaccines were reported, and we identified 25,219 AEFIs associated with autoimmune disorders following COVID-19 vaccination, including mRNA ($n=21,470$) and viral vector ($n=3366$) platforms in VigiBase. Descriptive characteristics of the COVID-19 vaccine-related events are presented in Table 1. Among those with available data, AEFIs were more likely to occur in females ($n=17,021$, 67.5%), and the number of AEFIs appeared to be two times higher in females than in males. The tendency for AEFI related to autoimmune disorders to be more prevalent in females was consistently observed in all other vaccine groups as well.

Compared with other age groups, patients aged 45–64 years were most likely to experience AEFIs related to autoimmune disorders following COVID-19 vaccination ($n=7281$, 39.5%). AEFIs have been reported in the Americas ($n=14,221$, 56.4%) and Europe ($n=10,376$, 41.1%). Nearly half of the reported AEFI cases ($n=11,581$, 45.9%) occurred within 7 days after vaccination. A significant number of patients with AEFI did not recover ($n=5261$, 20.9%) or had sequelae ($n=655$, 2.6%).

We detected the potential safety signal of disproportionality of four AEFIs following COVID-19 vaccination, including ankylosing spondylitis or psoriatic arthritis (ROR 1.86; 95% CI 1.53–2.27), IBD (ROR 1.77; 95% CI 1.60–1.96), polymyalgia rheumatica (ROR 1.42; 95% CI 1.30–1.55), and thyroiditis (ROR 1.40; 95% CI 1.30–1.50), with positive IC_{025} values (Table 2). We depicted the quantities and ROR values of each AEFI visually in Fig. S1. Moreover, A comparison of the occurrence of AEFIs according to vaccine type is shown in Table S1.

Overall, AEFIs of more than 40% had co-reported AEs. Among these, the top co-reported AEs included musculoskeletal and connective tissue disorders (2327/25,219, 9%, i.e., arthralgia, myalgia, and arthritis), nervous system disorders (1305/25,219, 5%, i.e., headache, facial paralysis, and Guillain-Barre syndrome), and skin and subcutaneous

Table 1 Baseline characteristics of reported AEFIs with COVID-19 vaccines as suspected or interacting drug in VigiBase

Characteristic	COVID-19 vaccines ($n = 25,219$)	All other vaccines ($n = 14,972$)
Sex		
Male	8030 (31.8)	5455 (36.4)
Female	17,021 (67.5)	9139 (61.1)
Missing	168 (0.7)	378 (2.5)
Age group		
< 18 years	586 (3.2)	6289 (47.3)
18–44 years	5857 (31.8)	3594 (27.0)
45–64 years	7281 (39.5)	1906 (14.3)
65–74 years	2953 (16.0)	976 (7.3)
≥ 75 years	1747 (9.5)	531 (4.0)
Missing	6795 (26.9)	1676 (10.1)
Region		
Africa	29 (0.1)	19 (0.1)
America	14,221 (56.4)	7.633 (51.1)
Asia	76 (0.3)	26 (0.3)
Oceania	517 (2.1)	1219 (8.1)
Europe	10,376 (41.1)	6075 (40.5)
Vaccine type		
BNT162b2	17,326 (68.7)	-
mRNA-1273	4144 (16.4)	-
Ad26.COV2.S	597 (2.3)	-
ChAdOxI nCov-19	2769 (10.9)	-
Time to onset (days)		
0–7	11,581 (45.9)	4913 (32.8)
8–14	2884 (11.4)	1795 (12.0)
15–21	1684 (6.7)	1187 (7.9)
22–28	1172 (4.6)	737 (4.9)
> 28	4897 (19.4)	4556 (30.4)
Reaction outcome		
Recovered/recovering	5369 (21.3)	4261 (28.5)
Not recovered	5261 (20.9)	2677 (17.9)
Recovered with sequelae	655 (2.6)	395 (2.6)
Fatal	7 (0.0)	47 (0.3)
Missing	13,857 (54.9)	7583 (50.6)

AEFI adverse event following immunization

tissue disorders (762/25,219, 3%, i.e., rash, purpura, and psoriasis). The symptoms were temporary or long-term and ranged from mild to severe. The 40 most frequent intersections among the 10 SOCs are depicted in (Fig. 1).

Regarding co-reported drugs reported with COVID-19 vaccines, the most frequent drug classes were immunosuppressants (i.e., TNF-α inhibitors and interleukin inhibitors) ($n = 4248$, 16.8%), antineoplastic agents (i.e., CD20 inhibitors and Bruton's tyrosine kinase inhibitors) ($n = 1661$, 6.6%), and analgesics (i.e., paracetamol and aspirin) ($n = 1031$, 4.1%) (Fig. 2).

Among the 16 AEFIs following vaccination, 14 AEFIs were observed to manifest a tendency to occur shortly after vaccination, except for hemolytic anemia/idiopathic and ITP (Fig. 3). The median TTO was similar for the 14 AEFIs, ranging from 2 to 5 days. Most AEFIs for mixed connective tissue disorder, myasthenia gravis, polymyalgia rheumatica, thyroiditis, and type 1 diabetes occurred within 4 days of COVID-19 vaccination. In contrast, the median TTO for hemolytic anemia/idiopathic (median 10 days [IQR 3–16]) and ITP (median 9 days [IQR 2–15]) was longer than that for other AEFIs.

The results of the sensitivity analysis were consistent with our primary results, but polymyalgia rheumatica was not observed as a potential safety signal, unlike the main analysis results. The analysis in which the comparator was limited to the influenza vaccine and the analysis excluding the co-reported immunosuppressant showed increased reporting odds for the four AEFIs (Tables S2 and S3).

Discussion

In this pharmacovigilance study, we investigated the potential safety signals of AEFIs related to autoimmune disorders following COVID-19 vaccination using the WHO global database, which included spontaneous reports of all potential AEFIs after vaccination. Validated methods were utilized, and the potential safety signals of the four AEFIs following COVID-19 vaccination were observed. The analysis showed that the risk of AEFIs after vaccination was significantly higher in females than in males, suggesting that sex differences may further influence this risk. The incidence of autoimmune disorders is documented to be twice as high in women compared with men, a trend consistent with findings from our study. Several heterogeneous mechanisms such as sex hormone effects and sex chromosome differences have been recognized, contributing to the gender bias favoring females in autoimmune disorders [22]. The sex hormone, specifically estrogen, has a broad impact, enhancing cellular activity and antibody production. This remains an active area of scholarly inquiry [23]. Sensitivity analyses involving AEFIs after influenza vaccination and reports excluding immunosuppressants support these findings.

Although COVID-19 vaccines have demonstrated a well-documented safety profile in randomized clinical trials for approval, several retrospective studies and case series have described AEFIs following vaccination since the launch of mass vaccination against COVID-19. Currently, in the literature, although few published studies have evaluated the risk of IBD after COVID-19 vaccination, an observational cohort

Table 2 AEFIs associated with the COVID-19 vaccine in VigiBase

	COVID-19 vaccine	All other vaccines	ROR (95% CI)	IC_{025}
AEFIs				
Ankylosing spondylitis or psoriatic arthritis	633	117	**1.86 (1.53–2.27)**	0.03
Hemolytic anemia/idiopathic	547	1451	0.13 (0.12–0.14)	−1.58
Idiopathic inflammatory myopathies	1298	1039	0.43 (0.40–0.47)	−0.52
ITP	1112	3046	0.13 (0.12–0.13)	−1.57
IBD	2290	445	**1.77 (1.60–1.96)**	0.09
Mixed connective tissue disorder	274	187	0.50 (0.42–0.61)	−0.54
Multiple sclerosis	2753	2221	0.43 (0.40–0.45)	−0.50
Myasthenia gravis	673	162	1.43 (1.20–1.70)	−0.03
Pernicious anemia	25	12	0.72 (0.36–1.43)	−0.86
Polymyalgia rheumatica	2398	581	**1.42 (1.30–1.55)**	0.03
Rheumatoid arthritis	5040	1617	1.07 (1.01–1.13)	−0.03
Sjogren's syndrome	293	134	0.75 (0.61–0.92)	−0.33
Systemic lupus erythematosus	1623	1254	0.44 (0.41–0.48)	−0.49
Thyroiditis	3527	867	**1.40 (1.30–1.50)**	0.04
Type1 diabetes	622	552	0.39 (0.35–0.43)	−0.63
Vasculitis	2111	1287	0.56 (0.53–0.60)	−0.34

Values in bold indicate the significance of values as a signal for AEFI following COVID-19 vaccination

AEFI adverse event following immunization, *ROR* reporting odds ratio, *IC* information component, *ITP* Idiopathic thrombocytopenic purpura, *IBD* Inflammatory bowel disease

study that used electronic medical records in Hong Kong found that COVID-19 vaccination did not increase the risk of IBD flare-ups (aIRR 0.69; 95% CI 0.35–1.36) [24]. In the US study, A minimal proportion of patients (2%) reported clinically significant IBD relapse following COVID-19 vaccination [25]. In contrast, a 22-year-old female experienced the

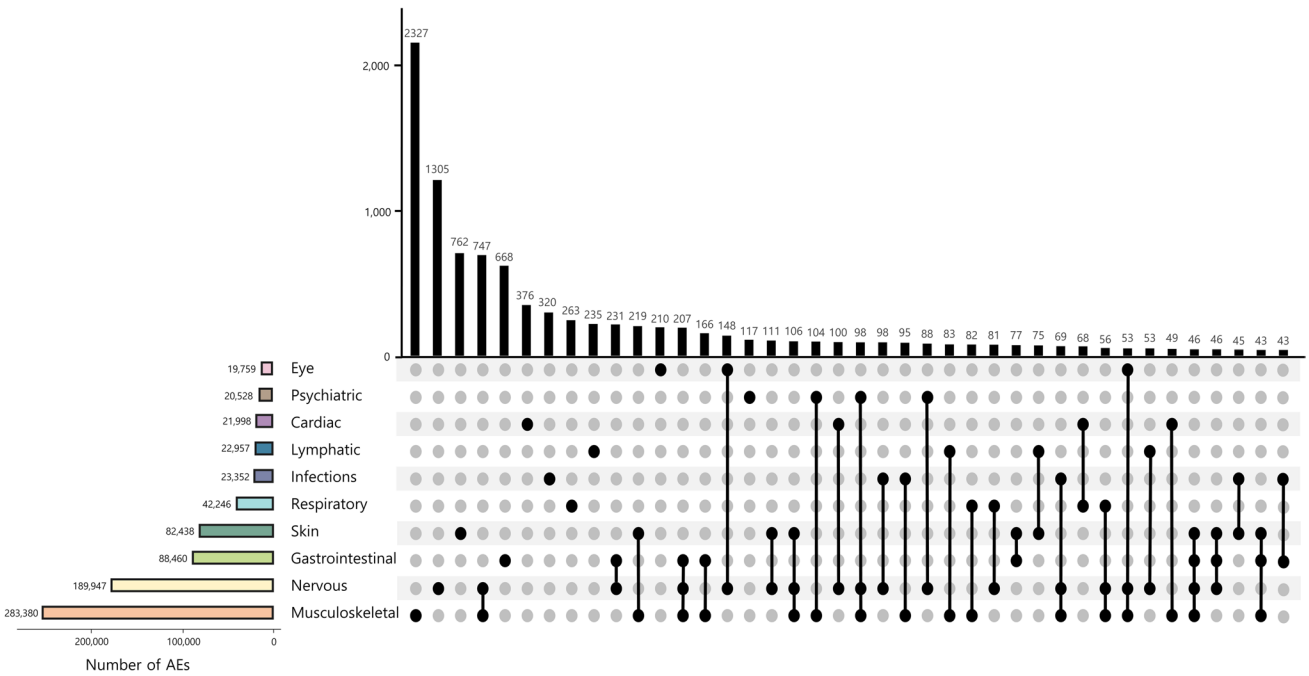

Fig. 1 The 40 most frequent co-reported adverse events in COVID-19 vaccine-associated AEFIs in VigiBase. *AE* adverse event. This presented co-reported AEs associated with AEFIs related to autoimmune disorders classified into ten SOC classes. The vertical bar graph displayed the total of co-reported AEs associated with AEFIs related to autoimmune disorders grouped by system organ class (SOC), highlighting the 40 most frequent intersections. Through the intersection of SOC, one can infer which organs frequently accompany AEFIs related to autoimmune disorders. Meanwhile, the horizontal bar graph presented the sum of drug-AE pairs for each respective SOC

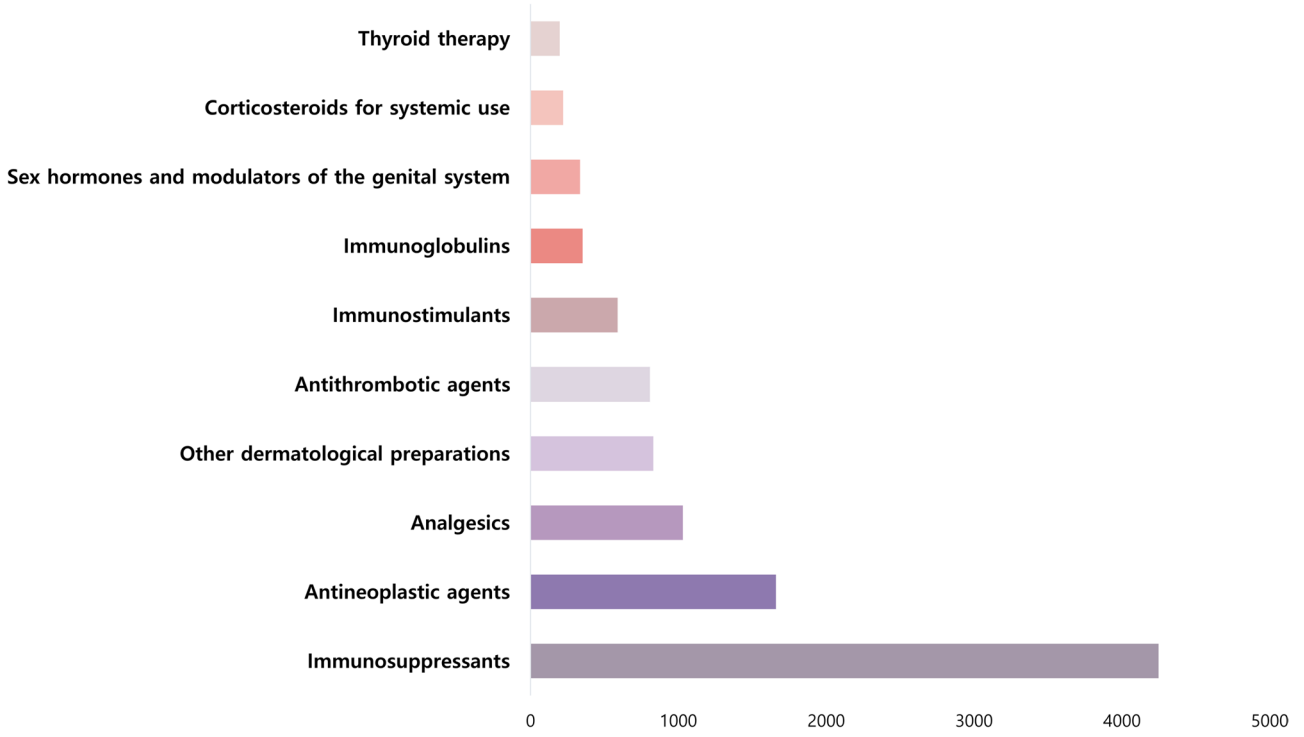

Fig. 2 The number of co-reported drugs with COVID-19 vaccines. The *x*-axis represented the number of drugs reported concurrently, as documented in AEFI related to autoimmune disorders reports associated with COVID-19 vaccines

relapse of ulcerative colitis 4 days following COVID-19 vaccination in Japan. Although the study identified COVID-19 vaccination as a potential trigger for ulcerative colitis flares, the immunopathogenesis of such flares remains insufficiently characterized [26]. Our study showed a significant relationship between IBD and COVID-19 vaccines. However, due to the unclear pathophysiological relationship between IBD and COVID-19 vaccines, further subsequent research is needed. Other pharmacovigilance studies reported an increased risk of polymyalgia rheumatica and thyroid disorders after COVID-19 vaccination (ROR 2.3; 95% CI 2.0–2.6, ROR 1.9; 95% CI 1.1–2.5, respectively) [27, 28]. These findings were consistent with our study, which showed higher odds of reporting these AEFIs. Further research will be needed to elucidate the differences in COVID-19 vaccination and AEFIs incidence between these countries.

COVID-19 vaccines may trigger incidence of AEFIs through the modification of the immune system and induce robust systemic immunity. Although vaccines activate humoral and cellular immune responses, rare cases of nonspecific activation of autoreactive lymphocytes have been reported, causing an abnormal immune response [29]. Since the safety profiles of next-generation vaccine platforms, such as mRNA, are not yet well characterized, close vaccine safety surveillance is warranted. Two theoretical bases explain the potential relationship between the COVID-19 vaccination and AEFIs. The molecular resemblance theory suggests that COVID-19 vaccines may exacerbate or initiate AEFIs owing to the similarity between the vaccine spike protein and some human tissue proteins [30]. Furthermore, the vaccine-stimulated pro-inflammatory response can cause immune system dysregulation, with the mRNA vaccine pathway particularly activating pro-inflammatory cytokines, such as type I interferon, which can lead to the loss of immune tolerance [31]. However, further studies are needed to address the association between AEFIs and COVID-19 vaccinations and the underlying mechanisms.

Several previous studies have reported the median TTO of AEFIs, such as multiple sclerosis and myasthenia gravis with a median of 1 day (IQR 0–3) [32], whereas cutaneous reactions, including purpura, are more likely to occur within 4 days (IQR 2.5–15) [33]. Our TTO analysis also showed that the period with the highest risk of AEFI was more likely to occur within 0–7 days following vaccination, with the greatest risks generally observed around 4 days following vaccination. Given the temporal association between symptom occurrence and COVID-19 vaccination, we hypothesized that vaccination could contribute to AEFIs. Therefore, close monitoring for the early detection and appropriate care of AEFIs is recommended during the first few days after vaccination.

AEFI related to autoimmune disorders	No. of cases with available time-to-onset data	Median time to AIDs onset (IQR), d
Ankylosing spondylitis or psoriatic arthritis	476	2 (1-7)
Hemolytic anemia / idiopathic	352	10 (3-16)
Idiopathic inflammatory myopathies	962	2 (0-8)
ITP	772	9 (2-15)
IBD	1631	2 (1-8)
Mixed connective tissue disorder	173	4 (1-12)
Multiple sclerosis	1829	2 (1-9)
Myasthenia gravis	452	4 (1-12)
Pernicious anemia	15	1 (0-5)
Polymyalgia rheumatica	1685	4 (1-11)
Rheumatoid arthritis	3577	3 (1-10)
Sjogren's syndrome	204	3 (1-12)
Systemic lupus erythematosus	1002	3 (1-11)
Thyroiditis	2278	4 (1-11)
Type1 diabetes	336	4 (1-16)
Vasculitis	1577	5 (1-12)

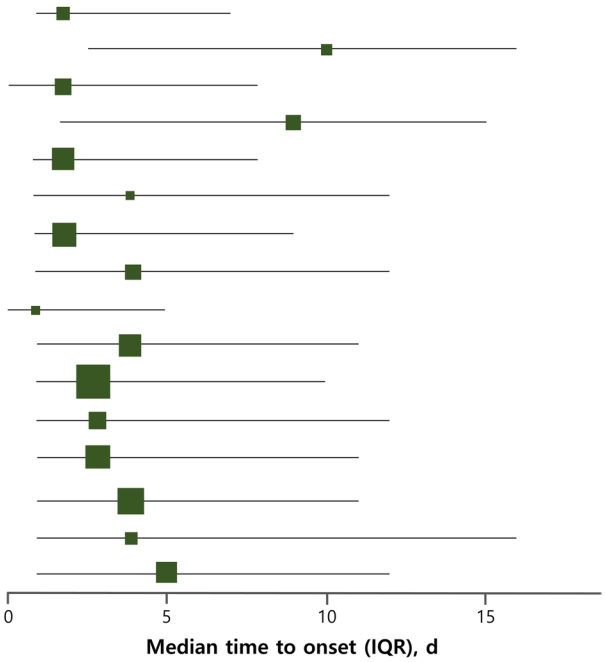

Fig. 3 Reported time-to-onset of AEFIs following COVID-19 vaccination from VigiBase. *AEFI* adverse event following immunization, *IQR* interquartile range, *ITP* idiopathic thrombocytopenic purpura, *IBD* inflammatory bowel disease

Co-reported AEs with COVID-19 vaccines include musculoskeletal and connective tissue disorders such as arthralgia, myalgia, and nervous system disorders [34–36]. In particular, the mRNA vaccines are associated with more severe symptoms of musculoskeletal and connective tissue disorders [37]. These two commonly co-reported AEs were simultaneously described in 747 AEFIs reports, making it the fourth most frequently reported overlap. A better understanding of these co-reported AEs is necessary, and additional vaccine safety surveillance is required to manage their wide-ranging effects.

When evaluating the safety of COVID-19 vaccines, caution should be exercised regarding co-reported drugs, such as immunosuppressants and antineoplastic agents. TNF-α inhibitors and rituximab, among other co-reported drugs, can modulate the humoral immune response after vaccination, and their effects on vaccinated individuals need to be investigated [38]. Although concerns about vaccination in patients receiving immunosuppressants have been raised, the current literature has only assessed serological responses to COVID-19 vaccination [39]. Further studies are necessary to clarify the potential interactions or close relationship between immunosuppressants and COVID-19 vaccines.

Our study raised awareness about the potential safety signals of AEFIs following COVID-19 vaccination by comprehensively assessing diverse forms of AEFI using the largest pharmacovigilance database of its kind. The large-scale database provided opportunities to assess rare AEFIs that could not be identified through trials, and disproportionality analysis on VigiBase was the most suitable for detecting the risk of undesirable AEs. However, this study has some limitations. First, quantitative signal detection through spontaneous reporting databases like the VigiBase encounters inherent limitations, including missing information, varying quality of individual case safety reports, duplication in reporting, and under-reporting due to lack of awareness. Consequently, our findings should not be interpreted as indicating a casual relationship between COVID-19 vaccines and AEFIs. Further validation and assessment of potential safety signals are required for a more comprehensive understanding [40]. Actually, in the literature, the Ad26.COV2.S vaccine has been reported to be associated with AEFI related to autoimmune disorders, including Guillain-Barré syndrome; however, we were unable to perform subgroup analyses related to the Ad26.COV2.S vaccine in this study due to an insufficient number of reports. Nevertheless, the main results of this study provide evidence for developing hypotheses for further research. Second, the characteristics of the recipients of COVID-19 vaccines may have differed from those of recipients of all other vaccines in unknown ways, which can

affect AEFIs risk. Concerns about unmeasured differences among vaccine recipients remain, and the results should be interpreted with caution. Lastly, although VigiBase is the largest pharmacovigilance database, the vaccine-related information used in this study was mostly reported from the USA and Europe. This variation can be attributed to the differing approval dates of COVID-19 vaccines across countries, highlighting the necessity for subsequent research on AEFIs gathered from a more extensive range of countries.

Conclusion

In response to the necessity of understanding AEFIs related to autoimmune disorders following COVID-19 vaccination, our study observed four potential safety signals, namely, ankylosing spondylitis or psoriatic arthritis, inflammatory bowel disease, polymyalgia rheumatica, and thyroiditis. However, further research is required to establish a causal relationship between COVID-19 vaccines and autoimmune disorders. Thus, our study highlights the importance of active safety surveillance to detect the four AEFIs related to autoimmune disorders following COVID-19 vaccination in light of the associated benefits.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-023-03618-w.

Author contribution S.K. designed the study, collected the data, performed the statistical analyses, interpreted the data, and wrote the manuscript. S.B. designed the study, interpreted the data, and contributed to the writing of the manuscript. S.A. and N.K. critically interpreted data and manuscript. J.Y.S. designed the study, supervised the statistical analyses and interpretation of the data, and critically revised the manuscript. J.Y.S., the guarantor of the study, accepts full responsibility for the results of this study, has access to the data, and controls the decision to publish. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been submitted.

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Availability of data and materials The data that support the findings of this study are available from Uppsala Monitoring Centre, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Uppsala Monitoring Centre.

Declarations

Ethics approval and consent to participate The institutional review board of Sungkyunkwan University approved the study (IRB No. SKKU 2023-02-038); the board waived the requirement for obtaining informed consent as this study used anonymized administrative data.

Conflict of interest The authors declare no competing interests.

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