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*Research Article*

# A Real-World Safety Analysis of Upadacitinib Based on FDA Adverse Event Reporting System (FAERS)

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*Objectives*. To investigate adverse events (AEs) associated with upadacitinib in the real world using data mining from the FDA Adverse Event Reporting System (FAERS). *Methods*. Disproportionality analysis, including the reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN), and the multiitem gamma Poisson shrinker (MGPS) algorithms, was used to quantify the signals of upadacitinib-associated AEs. *Results*. The study found 23683 reports of AEs associated with upadacitinib. A total of 149 substantial disproportionality preferred terms (PTs) that complied with all algorithms were identified. The infections discovered matched those mentioned in the specification and clinical trials, including pneumonia, upper respiratory tract infection, herpes zoster, and acne. Malignant and thrombotic AEs were also noted. Diverticulitis, myocardial infarction, transient ischaemic attack, and dysstasia were among the new AEs found. Upadacitinib-related AEs had a median onset time of 237 days and an interquartile range (IQR) of 78–509 days. *Conclusions*. The findings of our study were in line with clinical observations, and we also identified potential novel and unexpected AEs signals for upadacitinib, indicating the necessity for prospective clinical trials to corroborate these findings and demonstrate their link. Our results offered significant support for additional upadacitinib safety research.

## 1. Introduction

The Janus kinase/signal transduction and activator of transcription (JAK-STAT) pathway is a target in inflammation, which has a role in the pathogenesis of a number of autoimmune disorders, including rheumatoid arthritis (RA), atopic dermatitis, and psoriasis [1]. JAK inhibitors (JAKinibs) are small molecules that inhibit JAK kinase and disrupt the JAK-STAT pathway, thereby halting the progression of inflammatory disorders. Upadacitinib is a reversible JAKinibs that was initially approved by the United States Food and Drug Administration (FDA) on August 16, 2019 for the treatment of RA and subsequently approved for the treatment of psoriatic arthritis, atopic dermatitis, ulcerative colitis, and ankylosing spondylitis based on clinical trials [2–6].

Upadacitinib has been shown to be effective, but according to clinical trials and patients receiving JAKinibs, it is linked to three FDA "black box" warnings: serious infections, malignancy, and thrombosis [7]. The most frequent adverse reactions of upadacitinib were upper respiratory tract infections, nausea, cough, and pyrexia. Other adverse reactions, which were reported in less than 1% of patients, included pneumonia, herpes zoster, herpes simplex (including oral herpes), and oral candidiasis. Systematic research on upadacitinib-related ADRs based on the real world is lacking.

In this study, adverse events (AEs) related to upadacitinib were retrospectively analyzed from the FDA Adverse Event Reporting System (FAERS). FAERS is a database that is accessible to the general public and contains reports of AEs associated with drugs, biologics, and certain other medicinal products. We can obtain adverse events of target drug through datamining of FAERS and can conduct follow-up analysis [8]. In this study, we conducted a retrospective analysis of the AEs associated with upadacitinib from the third quarter of 2019 to the fourth quarter of 2022.

## 2. Methods

*2.1. Data Source.* We extracted all reports of AEs for upadacitinib using the generic name of "upadacitinib" and the brand name of "RINVOQ" from the FAERS database through the third quarter of 2019 to the fourth quarter of 2022. FAERS quarterly files contain drug information (DRUG), demographic and administrative information (DEMO), preferred terms (PTs) coded for the adverse event (REAC), report sources (RPSR), patient outcomes (OUTC), therapy start and end dates for reported drugs (THER), and indication for use (INDI). AEs in the quarterly files were coded by Medical Dictionary for Regulatory Activities 25.1 (MedDRA). The highest level of MedDRA is the system organ class (SOC), and we analyzed AEs for upadacitinib at both the SOC and PT levels. As a report may involve multiple drugs and multiple ADRs, drugs are assigned the role_codes of primary suspect (PS), secondary suspect (SS), concomitant (C), and interacting (I). In this study, reports of AEs were only taken into account if upadacitinib was listed as the PS role_code.

As an open availability database, FAERS data includes incomplete and duplicate reports. We remove all of duplicate reports following the FDA's recommendations by choosing the latest FDA_DT when the CASEIDs were the same and selecting the higher PRIMARYID when the CASEID and FDA_DT were the same.

We also evaluated the onset time of adverse events caused by upadacitinib. The onset time was the period between EVENT DT (adverse event onset date) and START DT (the date of upadacitinib initiation); incorrect date entries and missing particular data were removed. The flowchart of our study is shown in Figure 1.

*2.2. Statistical Analysis.* The statistical analysis of this study was conducted using MYSQL software version 8.0. Descriptive analysis was used to summarize the clinical characteristics of all AEs regarding to upadacitinib.

Disproportionality analysis was performed to identify positive signals between upadacitinib and all AEs. Calculations of measures of disproportionality are primarily based upon a two-by-two contingency table (Supplementary Table S1). In quantitative signal detection, a combination of upadacitinib and an AE that are disproportionately highly represented in the FAERS database presents an important signal based on a difference from the background frequency [9]. Both Frequentist and Bayesian methods in the disproportionality analysis were applied to investigate the correlation between an AE and upadacitinib, using the reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN), and the multiitem gamma Poisson shrinker (MGPS). To improve the accuracy of signals and eliminate false positive PTs, the adverse reaction was judged to be valid when the results of all four algorithms were positive in our study. The formulas for the four algorithms are shown in Supplementary Table S2.

## 3. Results

*3.1. Descriptive Results.* From the third quarter of 2019 to the fourth quarter of 2022, a total of 6317606 AEs were submitted to the FAERS database, among which 23683 AEs of upadacitinib were reported. The characteristics of AEs with upadacitinib are presented in Table 1. Females (72.63%) made up a substantial proportion of the AEs, and the ratio of females to males was approximately 3~5 : 1, which is consistent with the epidemiological data of RA [10]. Patients older than 40 years accounted for the majority of AEs. RA was the most reported indication (63.45%), followed by COVID-19 immunisation (21.58%). The most often reported severe result was other serious medical events (36.76%), followed by hospitalization (20.57%) and death (3.26%). Most of the AEs were reported from the US (74.42%). A substantial proportion of AEs were submitted by the consumer (76.41%). The number of AEs had gradually increased from 2019 to 2022, with the proportion of 66.98% reported in 2022, possibly due to the COVID-19 pandemic.

*3.2. Signal Detection.* Signal reports of upadacitinib at the SOC level are shown in Table 2. The significant SOCs were "Musculoskeletal and connective tissue disorders (SOC: 10028395)," "Infections and infestations (SOC: 10021881)," "Surgical and medical procedures (SOC: 10042613)," and "Social circumstances (SOC: 10041244)."

A total of 149 significant PTs are shown in Table 3. The appearance of "Upper respiratory tract infection (PT: 10046306)," "Nasopharyngitis (PT: 10028810)," "Herpes zoster (PT: 10019974)" are in line with the instructions. Signals related to the FDA "black box" warnings were presented as "Pneumonia (PT: 10035664)," "Malignant melanoma (PT: 10025650)," "Thrombosis (PT: 10043607)," "Pulmonary thrombosis (PT: 10037437)" and "Myocardial infarction (PT: 10028596)." Notable unexpected AEs discovered included "Diverticulitis (PT: 10013538)," "Chronic obstructive pulmonary disease (PT: 10009033)," "Pulmonary fibrosis (PT: 10037383)," "Dysstasia (PT: 10050256)," and "Hypophagia (PT: 10063743)." In addition, COVID-19-related AEs, including "COVID-19 (PT: 10084268)," "COVID-19 pneumonia (PT: 10084380)," and "SARS-CoV-2 test positive (PT: 10084271)," are noteworthy. However, both "Anaemia (PT: 10002034)" and "Hepatitis B reactivation (PT: 10058827)," which are listed in the drug label, failed to meet the criteria for significant signals.

*3.3. Onset Time Events.* The onset times of upadacitinib-associated AEs are shown in Figure 2. A total of 8185 upadacitinib-associated AEs reported an onset time, with the median onset time of 237 days and the interquartile range (IQR) of 78–509 days. The findings revealed that the incidence of AEs was high in the first month of administration ($n = 1137$, 4.80%) and then slowly decreased over time, but still a sizable number of AEs continued to occur after one year of upadacitinib treatment ($n = 2835$, 11.97%).

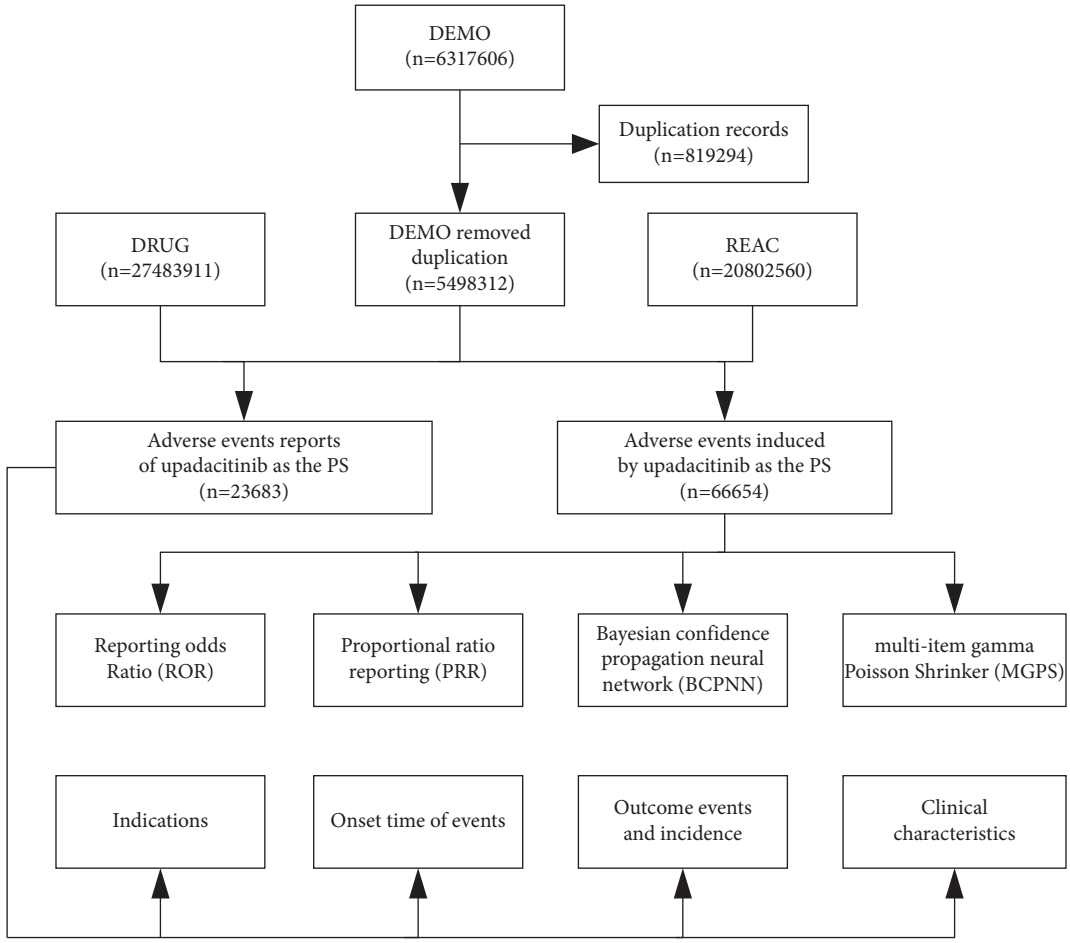


Figure 1: The flow diagram of selecting upadacitinib-associated AEs from FAERS database.

## 4. Discussion

JAKinibs, a class of targeted synthetic pharmacological drugs, are the newest therapeutic approach to RA approved by the FDA. Compared with conventional synthetic and biologic agents, JAKinibs have the advantage of oral administration [11]. Upadacitinib, as the second-generation JAKinibs, has the ability to specifically block JAK1 signaling. The real-world safety studies of JAKinibs are mostly concerned with the AEs of thrombosis, and upadacitinib's AEs reports are insufficient because of its short time to market [12, 13]. This study comprehensively investigated the real-world safety of upadacitinib based on extensive reports of the FAERS database.

The sex ratio of upadacitinib-related AEs corresponds to the incidence of RA, with females having a three- to five-fold higher prevalence than males [10]. Genes and hormonal changes may be responsible for this phenomenon. According to studies, RA activity in pregnant women spontaneously improves and then relapses after delivery, proving that estrogens have a preventative effect on the development of RA [14]. In addition, the highest incidence of RA occurs between the ages of 45 and 55, during the perimenopausal years, which further supports a link between the beginning of RA and an estrogen deficiency [15]. According to our findings, the majority of cases across all cases with known ages were above 40 years old, which is consistent with the peak onset age for RA.

The disproportionality analysis revealed that "Musculoskeletal and connective tissue disorders," "Surgical and medical procedures," and "Infections and infestations" were the most frequent and significant AEs of upadacitinib at the SOC level. The first two AEs were most likely brought on by the progression of RA, which weakens bones and damages cartilage [16]. Infection is primarily an adverse reaction to upadacitinib, we found 26 PTs of "infections and infestations," almost all of which had been pointed out on labels and in clinical trials, including upper respiratory tract infection, influenza, pneumonia, kidney infection, eye infection, gastroenteritis viral, and herpes zoster. This highlighted how accurate and significant our results were.

In 26 PTs, "COVID-19" was the most frequent medical conditions, and "COVID-19 pneumonia" was one of its major associated infections. Due to the immunosuppression caused by upadacitinib and in line with the findings of a clinical study for upadacitinib in PsA that was undertaken during the COVID-19 pandemic [17], it is possible to predict that this discovery will occur during the breakout of a new coronavirus. In addition, due to their impaired immune systems, RA patients are more likely to get the COVID-19

Table 1: Clinical characteristics of reports with upadacitinib from the FAERS database.

| Number of events | 23683 |
|---|---|
| Gender | |
| Female | 17202 (72.63%) |
| Male | 5260 (22.21%) |
| Unknown | 1221 (5.16%) |
| Age (years) | |
| <20 | 112 (0.47%) |
| 20≤ and <40 | 733 (3.10%) |
| ≥40 | 9478 (40.02) |
| Unknown | 13360 (56.41%) |
| Indications (top four) | |
| Rheumatoid arthritis | 21085 (63.45%) |
| COVID-19 immunisation | 7172 (21.58%) |
| Psoriatic arthropathy | 1154 (3.47%) |
| Dermatitis atopic | 1012 (3.05%) |
| Serious outcome | |
| Other serious medical events | 8707 (36.76%) |
| Hospitalization | 4872 (20.57%) |
| Death | 773 (3.26%) |
| Disability | 226 (0.95%) |
| Life-threatening | 140 (0.59%) |
| Required intervention to prevent permanent impairment/damage | 13 (0.05%) |
| Congenital anomaly | 4 (0.02%) |
| Reported countries (top five) | |
| US (America) | 17626 (74.42%) |
| CA (Canada) | 1681 (7.10%) |
| BR (Brazil) | 650 (2.74%) |
| DE (Germany) | 626 (2.64%) |
| JP (Japan) | 412 (1.74%) |
| FR (France) | 144 (0.61%) |
| Reported person | |
| Consumer | 18097 (76.41%) |
| Physician | 2398 (10.13%) |
| Pharmacist | 2039 (8.61%) |
| Other health-professional | 11 (0.05%) |
| Lawyer | 1 (<0.01%) |
| Reporting year | |
| 2022 | 15864 (66.98%) |
| 2021 | 5351 (22.59%) |
| 2020 | 2302 (9.72%) |
| 2019 | 164 (0.69%) |

infection [18]. Intriguingly, "COVID-19 immunisation" was the second upadacitinib indication in our results, as shown in Table 1. We believe this was due to the suggestion of vaccination prior to the start of upadacitinib treatment [19, 20]. In addition, a number of drugs commonly used to treat RA have been proposed as potential treatments for COVID-19 since it has been revealed that both RA and COVID-19 infection share the same molecular pathway of an abnormal immune response [19]. For instance, baricitinib has demonstrated the ability to significantly reduce the host inflammatory response of CRS caused by COVID-19 infection [21]. However, the JAK/STAT inhibition caused by baricitinib impairs the antiviral response, potentially hastening the spread of the COVID-19 infection. Our findings precisely validate this in the absence of information on upadacitinib's potential impact on coronavirus infection.

Among the opportunity infections, herpes zoster is the most recognized infection complication with JAK inhibitors. Clinical trials for upadacitinib have shown that herpes zoster infections are more frequent with upadacitinib compared with placebo, csDMARDs, and biologics. Also, most of the cases were nonserious, very few serious cases occurred in the high-dose group of upadacitinib [22–24]. In our findings, herpes zoster also played an essential part in infections associated with upadacitinib. In addition, we kept an eye out for postherpetic neuralgia, a serious herpes zoster sequela that was validated by three of our four algorithms, with PRR being the exception. Gastrointestinal perforation has been listed as a warning in the label of upadacitinib. PTs such as "gastric perforation," "intestinal perforation," and "gastrointestinal perforation" did not appear in our results, because they did not confirm with the algorithm of PRR. However, we just discovered related PT as "diverticulitis." Diverticular disease is one of the most common diseases related to the gastrointestinal tract in Western countries and has been previously identified as a risk factor for gastrointestinal perforation in RA patients treated with tocilizumab therapy [25]. Diverticulitis was thus a notable AE associated with upadacitinib.

In the clinical trials with upadacitinib, malignancies, particularly cutaneous malignancies, are frequently observed. Our findings amply supported this since we only found skin cancer, basal cell carcinoma, squamous cell carcinoma of the skin, and malignant melanoma. The medicine label also lists lymphoma, but it was not identified in our findings. Unsurprisingly, in clinical trials for upadacitinib in psoriatic arthritis and ulcerative colitis, no cases of lymphoma have been reported [17, 24]. In addition, in the clinical trial for upadacitinib in RA, the exposure-adjusted event rate (EAER) of lymphoma was <0.1/100 PY (per 100 patient years) in both the 15 mg and 30 mg upadacitinib groups, which is lower than that of basal cell carcinoma (0.2E/100 PY) and squamous cell carcinoma of the skin (0.1E/100 PY) [23]. These findings might suggest that upadacitinib has a stronger association with malignancies of the skin than lymphoma.

Thrombosis is a nonnegligible AE associated with JAKinibs, previous research studies based on FAERS have identified pulmonary embolism, thrombosis, and deep vein thrombosis (DVT) associated with upadacitinib [12, 13]. In clinical trial in RA, there was no evidence of a dose relationship in DVT rates with upadacitinib or a pattern of time-to-DVT-onset [23]. In this study, myocardial infarction and transient ischaemic attack, major adverse cardiovascular events (MACEs), were newly identified. This discovery expanded the evidence on the "black box" warning.

The eczema herpeticum and acne that have been seen in upadacitinib trials for AD were also included in our findings. Eczema herpeticum has been found as the only type of opportunistic infection in the upadacitinib clinical trial for AD. In addition, acne is seen more frequently in AD studies for upadacitinib compared to earlier trials with JAKinibs in RA [2, 3]. These observations might indicate the association of eczema herpeticum and acne with the underlying AD condition.

Table 2: Signal strength of AEs of upadacitinib at the system organ class (SOC) level in FAERS database.

| SOC | *N* | ROR (95% one-sided CI) | PRR ($\chi^2$) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|
| General disorders and administration site conditions | 11072 | 1.23 (1.21) | 1.19 (17884.46) | 0.25 (0.22) | 1.19 (1.17) |
| Musculoskeletal and connective tissue disorders[a] | 10720 | 4.54 (4.45) | 3.97 (313384.06) | 1.97 (1.94) | 3.94 (3.87) |
| Infections and infestations[a] | 8426 | 3.22 (3.15) | 2.94 (151011.89) | 1.54 (1.51) | 2.92 (2.87) |
| Surgical and medical procedures[a] | 4704 | 7.06 (6.85) | 6.63 (75323.39) | 2.7 (2.66) | 6.52 (6.35) |
| Injury, poisoning, and procedural complications | 4416 | 0.69 (0.67) | 0.71 (16018.45) | −0.49 (−0.53) | 0.71 (0.69) |
| Gastrointestinal disorders | 4060 | 0.98 (0.95) | 0.98 (24.55) | −0.03 (−0.08) | 0.98 (0.95) |
| Nervous system disorders | 4026 | 1.04 (1.01) | 1.04 (149.02) | 0.06 (0.01) | 1.04 (1.01) |
| Investigations | 3443 | 1.1 (1.07) | 1.1 (511.71) | 0.14 (0.09) | 1.1 (1.07) |
| Skin and subcutaneous tissue disorders | 3108 | 1.01 (0.97) | 1.01 (4.8) | 0.01 (−0.04) | 1.01 (0.98) |
| Respiratory, thoracic, and mediastinal disorders | 2907 | 1.22 (1.18) | 1.21 (1329.35) | 0.28 (0.23) | 1.21 (1.18) |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | 1333 | 0.54 (0.51) | 0.55 (5667.02) | −0.86 (−0.94) | 0.55 (0.52) |
| Eye disorders | 1176 | 1.2 (1.13) | 1.19 (177.88) | 0.25 (0.17) | 1.19 (1.14) |
| Psychiatric disorders | 1132 | 0.37 (0.35) | 0.38 (15636.93) | −1.37 (−1.46) | 0.38 (0.36) |
| Cardiac disorders | 1117 | 1.07 (1.01) | 1.07 (27.14) | 0.1 (0.01) | 1.07 (1.02) |
| Vascular disorders | 1092 | 1.1 (1.04) | 1.1 (51.1) | 0.14 (0.05) | 1.1 (1.05) |
| Metabolism and nutrition disorders | 719 | 0.7 (0.65) | 0.71 (400.51) | −0.49 (−0.6) | 0.71 (0.67) |
| Renal and urinary disorders | 693 | 0.62 (0.57) | 0.62 (815.32) | −0.68 (−0.79) | 0.62 (0.58) |
| Social circumstances[a] | 562 | 2.28 (2.09) | 2.26 (462.9) | 1.17 (1.05) | 2.26 (2.1) |
| Immune system disorders | 435 | 0.7 (0.63) | 0.7 (160.58) | −0.51 (−0.65) | 0.7 (0.64) |
| Blood and lymphatic system disorders | 427 | 0.47 (0.43) | 0.48 (997.85) | −1.06 (−1.19) | 0.48 (0.44) |
| Hepatobiliary disorders | 305 | 0.72 (0.64) | 0.72 (64.17) | −0.47 (−0.63) | 0.72 (0.65) |
| Ear and labyrinth disorders | 302 | 1.41 (1.26) | 1.41 (36.32) | 0.49 (0.33) | 1.4 (1.28) |
| Reproductive system and breast disorders | 236 | 0.69 (0.61) | 0.69 (49.02) | −0.52 (−0.71) | 0.69 (0.62) |
| Product issues | 89 | 0.09 (0.07) | 0.09 (3332.65) | −3.38 (−3.67) | 0.09 (0.08) |
| Endocrine disorders | 86 | 0.63 (0.51) | 0.63 (11.13) | −0.65 (−0.95) | 0.63 (0.53) |
| Pregnancy, puerperium, and perinatal conditions | 35 | 0.18 (0.13) | 0.18 (114.07) | −2.45 (−2.89) | 0.18 (0.13) |
| Congenital, familial, and genetic disorders | 33 | 0.22 (0.15) | 0.22 (62.32) | −2.17 (−2.62) | 0.22 (0.16) |

*Notes*: [a]indicates statistically significant signals with four algorithms.

Table 3: Signal strength of reports of upadacitinib at the preferred terms level in FAERS database.

| SOC | Preferred terms (PTs) | *N* | ROR (95% one-sided CI) | PRR ($\chi^2$) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| Infections and infestations | COVID-19 | 1719 | 5.39 (5.14) | 5.28 (9105.87) | 2.38 (2.31) | 5.21 (5) |
| | Urinary tract infection | 630 | 4.43 (4.09) | 4.4 (1108.22) | 2.12 (2.01) | 4.35 (4.07) |
| | Pneumonia | 574 | 2.22 (2.05) | 2.21 (463.05) | 1.14 (1.02) | 2.2 (2.06) |
| | Nasopharyngitis | 461 | 3.11 (2.84) | 3.1 (456.05) | 1.62 (1.49) | 3.08 (2.85) |
| | Herpes zoster | 398 | 7.73 (7) | 7.69 (560.05) | 2.91 (2.77) | 7.53 (6.93) |
| | Infection | 350 | 2.77 (2.49) | 2.76 (233.1) | 1.46 (1.31) | 2.75 (2.51) |
| | Sinusitis | 343 | 4.01 (3.6) | 3.99 (308.91) | 1.98 (1.83) | 3.95 (3.62) |
| | Influenza | 269 | 3.25 (2.89) | 3.25 (161.88) | 1.69 (1.52) | 3.22 (2.91) |
| | Bronchitis | 174 | 3.29 (2.83) | 3.28 (68.35) | 1.7 (1.49) | 3.26 (2.87) |
| | Upper respiratory tract infection | 144 | 4.33 (3.67) | 4.32 (57.17) | 2.1 (1.86) | 4.27 (3.72) |
| | Localised infection | 131 | 5.93 (4.99) | 5.92 (55.35) | 2.54 (2.3) | 5.83 (5.05) |
| | Diverticulitis* | 121 | 5.2 (4.34) | 5.19 (44.56) | 2.36 (2.1) | 5.12 (4.41) |
| | Ear infection | 100 | 4.51 (3.71) | 4.51 (28.28) | 2.16 (1.88) | 4.46 (3.78) |
| | COVID-19 pneumonia | 98 | 3.95 (3.24) | 3.95 (25) | 1.97 (1.69) | 3.91 (3.31) |
| | Cystitis | 98 | 3.69 (3.02) | 3.69 (23.82) | 1.87 (1.59) | 3.66 (3.09) |
| | Kidney infection | 94 | 5.2 (4.24) | 5.19 (26.89) | 2.36 (2.07) | 5.12 (4.32) |
| | Oral herpes | 71 | 4.05 (3.21) | 4.05 (13.34) | 2 (1.67) | 4.01 (3.3) |
| | Staphylococcal infection | 71 | 3.21 (2.54) | 3.21 (11.14) | 1.67 (1.34) | 3.18 (2.62) |
| | Viral infection | 63 | 2.72 (2.12) | 2.72 (7.41) | 1.44 (1.09) | 2.71 (2.2) |
| | Postprocedural infection | 62 | 8.47 (6.58) | 8.47 (13.96) | 3.05 (2.68) | 8.27 (6.69) |
| | Tooth infection | 60 | 4.94 (3.83) | 4.94 (10.69) | 2.29 (1.93) | 4.88 (3.94) |
| | Respiratory tract infection | 55 | 2.65 (2.03) | 2.65 (5.48) | 1.4 (1.03) | 2.64 (2.11) |
| | Bacterial infection | 54 | 3.66 (2.8) | 3.66 (7.18) | 1.86 (1.48) | 3.63 (2.9) |
| | Postoperative wound infection | 45 | 7.33 (5.46) | 7.33 (7.05) | 2.84 (2.42) | 7.18 (5.61) |
| | Eye infection | 44 | 4.47 (3.32) | 4.47 (5.45) | 2.14 (1.72) | 4.42 (3.45) |
| | Gastroenteritis viral | 44 | 3.52 (2.62) | 3.52 (4.63) | 1.8 (1.39) | 3.49 (2.72) |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | Skin cancer | 153 | 4.88 (4.16) | 4.87 (69.02) | 2.27 (2.04) | 4.81 (4.21) |
| | Basal cell carcinoma | 71 | 5.01 (3.96) | 5 (15.07) | 2.3 (1.97) | 4.94 (4.06) |
| | Squamous cell carcinoma of skin | 50 | 9.54 (7.2) | 9.54 (9.35) | 3.21 (2.8) | 9.28 (7.33) |
| | Malignant melanoma | 46 | 3.37 (2.52) | 3.37 (4.88) | 1.74 (1.34) | 3.34 (2.62) |
| Cardiac disorders | Myocardial infarction* | 225 | 2.94 (2.58) | 2.94 (102.88) | 1.55 (1.36) | 2.92 (2.61) |
| Vascular disorders | Thrombosis | 229 | 3.35 (2.94) | 3.34 (120.29) | 1.73 (1.54) | 3.32 (2.97) |
| Respiratory, thoracic, and mediastinal disorders | Lung disorder | 104 | 2.59 (2.13) | 2.58 (18.98) | 1.36 (1.09) | 2.57 (2.19) |
| | Chronic obstructive pulmonary disease* | 99 | 2.63 (2.16) | 2.63 (17.56) | 1.39 (1.11) | 2.61 (2.21) |
| | Pulmonary thrombosis | 77 | 7.09 (5.66) | 7.09 (20.42) | 2.8 (2.47) | 6.95 (5.75) |
| | Pulmonary fibrosis* | 63 | 4.47 (3.49) | 4.47 (11.17) | 2.14 (1.79) | 4.42 (3.59) |
| | Respiratory disorder | 62 | 2.62 (2.04) | 2.62 (6.87) | 1.38 (1.04) | 2.61 (2.12) |
| | Sinus disorder | 60 | 3.61 (2.79) | 3.6 (8.77) | 1.84 (1.48) | 3.57 (2.89) |
| Metabolism and nutrition disorders | Hypophagia* | 55 | 2.83 (2.17) | 2.82 (5.89) | 1.49 (1.12) | 2.81 (2.25) |

Table 3: Continued.

| SOC | Preferred terms (PTs) | $N$ | ROR (95% one-sided CI) | PRR ($\chi^2$) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| Nervous system disorders | Cerebrovascular accident | 251 | 2.46 (2.17) | 2.46 (103.55) | 1.29 (1.11) | 2.45 (2.2) |
| | Carpal tunnel syndrome | 107 | 9.48 (7.82) | 9.47 (42.75) | 3.2 (2.93) | 9.22 (7.85) |
| | Sciatica | 83 | 6.58 (5.29) | 6.57 (23.12) | 2.69 (2.38) | 6.46 (5.38) |
| | Dysstasia* | 76 | 3.2 (2.55) | 3.2 (12.73) | 1.67 (1.35) | 3.17 (2.63) |
| | Nerve compression | 70 | 9.17 (7.23) | 9.16 (18.15) | 3.16 (2.81) | 8.93 (7.32) |
| | Transient ischaemic attack* | 56 | 3.1 (2.38) | 3.09 (6.71) | 1.62 (1.25) | 3.07 (2.47) |
| Skin and subcutaneous tissue disorders | Acne | 393 | 3.45 (3.12) | 3.44 (362.94) | 1.77 (1.63) | 3.41 (3.14) |
| | Dermatitis atopic | 125 | 3.41 (2.86) | 3.41 (36.41) | 1.76 (1.51) | 3.38 (2.92) |
| | Skin disorder | 120 | 4.18 (3.49) | 4.18 (38.89) | 2.05 (1.79) | 4.13 (3.55) |
| | Eczema | 94 | 2.67 (2.18) | 2.66 (16.09) | 1.41 (1.12) | 2.65 (2.23) |
| | Skin ulcer | 55 | 2.55 (1.96) | 2.55 (5.22) | 1.34 (0.98) | 2.54 (2.03) |
| Hepatobiliary disorders | Cholelithiasis* | 48 | 2.63 (1.98) | 2.63 (4.13) | 1.39 (0.99) | 2.62 (2.06) |
| Renal and urinary disorders | Nephrolithiasis | 136 | 3.37 (2.85) | 3.37 (42.68) | 1.74 (1.5) | 3.34 (2.9) |
| Eye disorders | Cataract | 325 | 6.62 (5.93) | 6.59 (355.04) | 2.7 (2.54) | 6.48 (5.91) |
| Gastrointestinal disorders | Gastric disorder | 110 | 3.15 (2.61) | 3.15 (26.33) | 1.65 (1.38) | 3.13 (2.67) |
| General disorders and administration site conditions | Pain | 2048 | 3.09 (2.96) | 3.03 (8864.88) | 1.59 (1.52) | 3.01 (2.9) |
| | Peripheral swelling | 630 | 3.79 (3.5) | 3.76 (1001.38) | 1.9 (1.79) | 3.73 (3.49) |
| | Illness | 467 | 3.7 (3.38) | 3.68 (541.4) | 1.87 (1.74) | 3.65 (3.38) |
| | Gait disturbance | 368 | 2.46 (2.22) | 2.45 (221.91) | 1.29 (1.14) | 2.44 (2.24) |
| | Unevaluable event | 283 | 4.56 (4.06) | 4.55 (227.7) | 2.17 (2) | 4.5 (4.08) |
| | Inflammation | 263 | 5.33 (4.72) | 5.32 (212.95) | 2.39 (2.22) | 5.24 (4.73) |
| | Swelling | 233 | 2.62 (2.3) | 2.61 (96.57) | 1.38 (1.19) | 2.6 (2.33) |
| | Gait inability | 186 | 4.39 (3.79) | 4.38 (96.18) | 2.11 (1.91) | 4.33 (3.84) |
| | Impaired healing | 95 | 3.99 (3.26) | 3.99 (23.65) | 1.98 (1.7) | 3.95 (3.33) |
| | Hernia | 72 | 4.37 (3.46) | 4.36 (14.38) | 2.11 (1.78) | 4.32 (3.55) |
| | Nodule | 61 | 5.44 (4.22) | 5.44 (11.57) | 2.42 (2.06) | 5.36 (4.34) |
| | Cyst | 54 | 5.18 (3.96) | 5.18 (8.86) | 2.35 (1.97) | 5.11 (4.08) |
| Immune system disorders | Immunodeficiency | 62 | 4.05 (3.15) | 4.05 (10.18) | 2 (1.65) | 4.01 (3.25) |

Table 3: Continued.

| SOC | Preferred terms (PTs) | $N$ | ROR (95% one-sided CI) | PRR ($\chi^2$) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| Injury, poisoning, and procedural complications | Fall | 839 | 3.23 (3.02) | 3.2 (1560.17) | 1.67 (1.57) | 3.18 (3) |
| | Procedural pain | 122 | 6.23 (5.2) | 6.22 (48.93) | 2.61 (2.36) | 6.11 (5.26) |
| | Hip fracture | 118 | 4.72 (3.94) | 4.72 (40.36) | 2.22 (1.96) | 4.66 (4) |
| | Postprocedural complication | 106 | 9.16 (7.55) | 9.15 (41.61) | 3.16 (2.88) | 8.91 (7.58) |
| | Upper limb fracture | 91 | 5.27 (4.28) | 5.26 (25.36) | 2.38 (2.08) | 5.19 (4.36) |
| | Road traffic accident | 86 | 2.92 (2.36) | 2.92 (14.92) | 1.54 (1.24) | 2.9 (2.43) |
| | Spinal fracture | 84 | 5.03 (4.05) | 5.02 (21.13) | 2.31 (2) | 4.96 (4.14) |
| | Limb injury | 82 | 3.1 (2.49) | 3.09 (14.38) | 1.62 (1.31) | 3.07 (2.56) |
| | Joint injury | 81 | 4.44 (3.56) | 4.44 (18.38) | 2.13 (1.82) | 4.39 (3.65) |
| | Ankle fracture | 80 | 6.29 (5.04) | 6.28 (21.12) | 2.63 (2.31) | 6.18 (5.13) |
| | Femur fracture | 76 | 4.25 (3.39) | 4.24 (15.76) | 2.07 (1.75) | 4.2 (3.48) |
| | Lower limb fracture | 74 | 5.02 (3.99) | 5.02 (16.39) | 2.31 (1.98) | 4.95 (4.09) |
| | Tendon rupture | 70 | 9.82 (7.74) | 9.81 (18.45) | 3.25 (2.91) | 9.54 (7.82) |
| | Head injury | 66 | 2.86 (2.24) | 2.85 (8.58) | 1.5 (1.17) | 2.84 (2.32) |
| | Rib fracture | 63 | 3.63 (2.83) | 3.62 (9.71) | 1.85 (1.5) | 3.59 (2.92) |
| | Foot fracture | 62 | 3.77 (2.94) | 3.77 (9.69) | 1.9 (1.55) | 3.74 (3.03) |
| | Meniscus injury | 59 | 10.38 (8.01) | 10.37 (13.27) | 3.33 (2.95) | 10.07 (8.1) |
| | Joint dislocation | 58 | 7.23 (5.57) | 7.22 (11.66) | 2.82 (2.45) | 7.08 (5.7) |
| | Wrist fracture | 45 | 4.57 (3.41) | 4.57 (5.77) | 2.18 (1.76) | 4.52 (3.53) |
| | Muscle strain | 43 | 5.99 (4.43) | 5.98 (5.99) | 2.56 (2.13) | 5.89 (4.57) |
| | Ligament sprain | 41 | 4.58 (3.36) | 4.57 (4.79) | 2.18 (1.74) | 4.52 (3.49) |
| | Pelvic fracture | 40 | 6.94 (5.08) | 6.94 (5.47) | 2.77 (2.31) | 6.81 (5.24) |
| | Back injury | 38 | 4.69 (3.41) | 4.69 (4.17) | 2.21 (1.76) | 4.64 (3.55) |
| Investigations | Blood cholesterol increased | 246 | 8.3 (7.31) | 8.27 (218.4) | 3.02 (2.83) | 8.09 (7.27) |
| | SARS-CoV-2 test positive | 185 | 6.14 (5.31) | 6.12 (111.88) | 2.59 (2.38) | 6.03 (5.33) |
| | Hepatic enzyme increased | 170 | 2.87 (2.47) | 2.86 (57.18) | 1.51 (1.29) | 2.85 (2.51) |
| | Grip strength decreased | 122 | 16.08 (13.4) | 16.05 (61.09) | 3.94 (3.67) | 15.32 (13.15) |
| | Inflammatory marker increased | 59 | 11.26 (8.68) | 11.25 (13.49) | 3.44 (3.06) | 10.89 (8.76) |
| | Product residue present | 46 | 5.83 (4.36) | 5.83 (6.78) | 2.52 (2.1) | 5.74 (4.5) |

Table 3: Continued.

| SOC | Preferred terms (PTs) | $N$ | ROR (95% one-sided CI) | PRR ($\chi^2$) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| Musculoskeletal and connective tissue disorders | Arthralgia | 1719 | 4.87 (4.64) | 4.77 (8660.33) | 2.24 (2.17) | 4.71 (4.52) |
| | Rheumatoid arthritis | 1318 | 11.03 (10.44) | 10.83 (6692.69) | 3.39 (3.31) | 10.5 (10.03) |
| | Pain in extremity | 1230 | 5.47 (5.16) | 5.38 (4697.75) | 2.41 (2.33) | 5.31 (5.06) |
| | Musculoskeletal stiffness | 650 | 8.04 (7.44) | 7.97 (1510.13) | 2.96 (2.85) | 7.8 (7.3) |
| | Back pain | 577 | 3.24 (2.98) | 3.22 (740.3) | 1.68 (1.56) | 3.2 (2.98) |
| | Joint swelling | 456 | 3.8 (3.46) | 3.78 (525.91) | 1.91 (1.77) | 3.75 (3.47) |
| | Mobility decreased | 390 | 6.38 (5.77) | 6.35 (504.31) | 2.64 (2.5) | 6.24 (5.74) |
| | Arthritis | 325 | 4.63 (4.15) | 4.61 (302.66) | 2.19 (2.03) | 4.56 (4.16) |
| | Osteoarthritis | 297 | 8.46 (7.54) | 8.43 (319.97) | 3.04 (2.88) | 8.23 (7.47) |
| | Arthropathy | 257 | 4.45 (3.93) | 4.43 (185.09) | 2.13 (1.96) | 4.39 (3.96) |
| | Joint range of motion decreased | 231 | 22.41 (19.61) | 22.34 (227.29) | 4.39 (4.19) | 20.91 (18.7) |
| | Musculoskeletal disorder | 197 | 12.51 (10.84) | 12.47 (153.29) | 3.59 (3.38) | 12.03 (10.68) |
| | Joint stiffness | 156 | 7.24 (6.18) | 7.23 (84.36) | 2.83 (2.6) | 7.09 (6.2) |
| | Intervertebral disc protrusion | 142 | 9.11 (7.7) | 9.09 (74.56) | 3.15 (2.91) | 8.86 (7.7) |
| | Systemic lupus erythematosus | 142 | 3.83 (3.25) | 3.83 (51.38) | 1.92 (1.69) | 3.79 (3.3) |
| | Neck pain | 139 | 3.2 (2.7) | 3.19 (42.55) | 1.66 (1.43) | 3.17 (2.76) |
| | Psoriatic arthropathy | 105 | 2.53 (2.09) | 2.53 (18.79) | 1.33 (1.06) | 2.51 (2.14) |
| | Rotator cuff syndrome | 87 | 9.91 (8.01) | 9.9 (28.56) | 3.27 (2.96) | 9.63 (8.05) |
| | Back disorder | 83 | 6.43 (5.17) | 6.42 (22.93) | 2.66 (2.35) | 6.31 (5.26) |
| | Fibromyalgia | 81 | 4.03 (3.23) | 4.02 (17.3) | 1.99 (1.69) | 3.98 (3.32) |
| | Foot deformity | 80 | 7.75 (6.21) | 7.75 (22.66) | 2.92 (2.6) | 7.58 (6.3) |
| | Exostosis | 54 | 8.77 (6.69) | 8.77 (10.68) | 3.1 (2.7) | 8.55 (6.82) |
| | Spinal stenosis | 52 | 7.38 (5.61) | 7.38 (9.43) | 2.85 (2.46) | 7.23 (5.74) |
| | Finger deformity | 47 | 11.59 (8.66) | 11.59 (8.61) | 3.49 (3.05) | 11.21 (8.78) |
| | Intervertebral disc degeneration | 47 | 6.66 (4.99) | 6.65 (7.44) | 2.71 (2.29) | 6.53 (5.13) |
| | Trigger finger | 44 | 12.36 (9.14) | 12.35 (7.63) | 3.58 (3.12) | 11.92 (9.26) |
| | Joint noise | 34 | 12.09 (8.59) | 12.09 (4.54) | 3.55 (3.02) | 11.67 (8.76) |
| | Joint lock | 32 | 15.76 (11.05) | 15.75 (4.19) | 3.91 (3.34) | 15.04 (11.17) |
| Social circumstances | Loss of personal independence in daily activities | 318 | 4.53 (4.05) | 4.51 (286.19) | 2.16 (2) | 4.46 (4.06) |
| | Bedridden | 47 | 4.86 (3.64) | 4.85 (6.5) | 2.26 (1.85) | 4.79 (3.77) |
| | Walking aid user | 41 | 9.39 (6.88) | 9.39 (6.26) | 3.19 (2.73) | 9.14 (7.05) |

Table 3: Continued.

| SOC | Preferred terms (PTs) | *N* | ROR (95% one-sided CI) | PRR ($\chi^2$) | IC (IC025) | EBGM (EBGM05) |
|---|---|---|---|---|---|---|
| Surgical and medical procedures | Therapy interrupted | 644 | 7.92 (7.32) | 7.85 (1476.08) | 2.94 (2.83) | 7.69 (7.2) |
| | Surgery | 627 | 13.87 (12.8) | 13.75 (1578.74) | 3.72 (3.61) | 13.21 (12.35) |
| | Knee arthroplasty | 400 | 24.85 (22.44) | 24.71 (687.74) | 4.52 (4.38) | 22.97 (21.08) |
| | Spinal operation | 302 | 25.47 (22.64) | 25.36 (392.85) | 4.56 (4.39) | 23.52 (21.32) |
| | Hip arthroplasty | 207 | 16.29 (14.17) | 16.25 (176.16) | 3.95 (3.75) | 15.49 (13.78) |
| | Knee operation | 202 | 26.83 (23.23) | 26.75 (176.5) | 4.63 (4.42) | 24.71 (21.91) |
| | Foot operation | 99 | 27.22 (22.16) | 27.18 (42.44) | 4.65 (4.34) | 25.08 (21.12) |
| | Limb operation | 99 | 26.8 (21.82) | 26.76 (42.39) | 4.63 (4.32) | 24.72 (20.81) |
| | Shoulder operation | 86 | 26.16 (20.99) | 26.13 (31.93) | 4.6 (4.26) | 24.18 (20.11) |
| | Hip surgery | 82 | 18 (14.4) | 17.98 (27.99) | 4.09 (3.76) | 17.05 (14.15) |
| | Shoulder arthroplasty | 74 | 36.24 (28.48) | 36.2 (24.17) | 5.02 (4.64) | 32.53 (26.59) |
| | Spinal fusion surgery | 58 | 20.29 (15.56) | 20.27 (14.19) | 4.26 (3.84) | 19.09 (15.29) |
| | Neck surgery | 53 | 25.46 (19.24) | 25.44 (12.1) | 4.56 (4.11) | 23.6 (18.67) |
| | Eye operation | 50 | 13.62 (10.26) | 13.61 (10.02) | 3.71 (3.28) | 13.08 (10.32) |
| | Hysterectomy | 44 | 8.18 (6.06) | 8.18 (6.96) | 3 (2.56) | 7.99 (6.22) |
| | Oral surgery | 43 | 25.74 (18.86) | 25.73 (7.97) | 4.58 (4.06) | 23.84 (18.37) |
| | Joint arthroplasty | 40 | 29.79 (21.53) | 29.77 (6.97) | 4.77 (4.22) | 27.26 (20.78) |
| | Cholecystectomy | 39 | 5.93 (4.32) | 5.93 (4.91) | 2.55 (2.09) | 5.84 (4.48) |
| | Tooth extraction | 39 | 4.75 (3.46) | 4.75 (4.42) | 2.23 (1.78) | 4.69 (3.6) |
| | Medical device implantation | 36 | 30.7 (21.8) | 30.68 (5.66) | 4.81 (4.21) | 28.02 (21.04) |
| | Dental operation | 36 | 20.79 (14.83) | 20.78 (5.48) | 4.29 (3.74) | 19.54 (14.73) |
| | Ankle operation | 31 | 26.88 (18.62) | 26.86 (4.16) | 4.63 (3.99) | 24.81 (18.25) |

*Note*. *New and significant signals of upadacitinib-associated AEs from FAERS database.

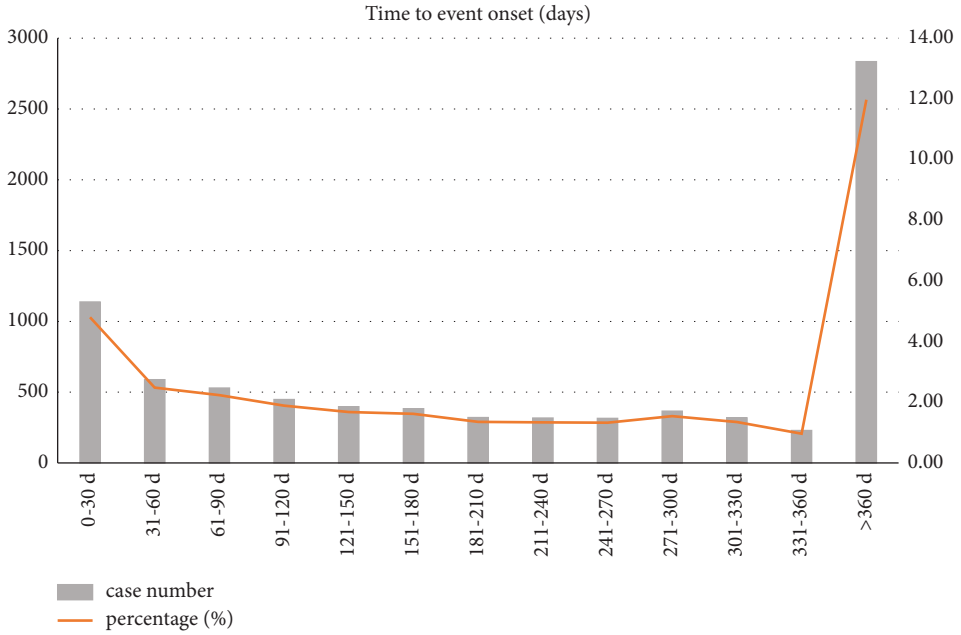


Figure 2: Time to onset of upadacitinib-associated AEs.

We also discovered the AE of systemic lupus erythematosus (SLE) related with upadacitinib, which has been shown to be significantly alleviated by baricitinib through downregulating key cytokines [26, 27]. The connection between JAKinibs and SLE requires more research because both RA and SLE are immune-mediated diseases and may share some underlying immunologic processes, such as dysregulated neutrophil activation and overproduction of inflammatory cytokines [28]. AEs of pulmonary fibrosis and chronic obstructive pulmonary disease were also detected; we considered them as comorbidities of RA. Lung diseases are the most common extra-articular manifestation of RA and can affect up to 60% of patients with RA during the disease course [29, 30]. Now that it is unclear whether the lung manifestations of RA are present at the outset or indeed precede the articular manifestations of the disease, more research studies are needed in the future study.

According to our findings, dysstasia, a new adverse event (AE) with upadacitinib, was found in nervous system conditions. Previous investigations have noted loss of consciousness, depression, and suicidality [13]. In addition, we just discovered hypophagia related to upadacitinib, which may be connected to neurological problems and calls for additional investigation.

We firstly analyzed the onset time of AEs with upadacitinib and found that most of the cases occurred within the first month ($n = 1137$, 4.80%) and a year later ($n = 2835$, 11.97%) after upadacitinib initiation. And in the first year, the occurrence of AEs had a downtrend as the duration of upadacitinib continues. Therefore, a longer follow-up period is required to monitor the ADRs of upadacitinib in clinical studies.

## 5. Limitations

Although the current study showed a potentially insightful relationship between the use of upadacitinib and the odds of reporting AEs in the FAERS, there are some limitations. First, the FAERS case report is voluntary and the case quality might be variable. In this study, reports of upadacitinib from consumers occupied 76.41%, this showed that consumers are very concerned about upadacitinib, but it is undeniable that the description of AEs may not be ample from consumers lacking medical education background, which results in inevitable bias. Second, some elements which might affect AEs with upadacitinib were not analyzed, like potential drug-drug interactions, drug combinations, and comorbidities. Thus, we were unable to infer an exact causal relationship between AEs and upadacitinib. Third, the disproportionality analysis only provides an estimation of the signal strength and can only yield statistical differences. Prospective clinical studies are still needed to confirm the causal relationship between them.

## 6. Conclusion

In conclusion, the present study scientifically and systematically assessed the safety signals of upadacitinib using the FAERS pharmacovigilance database. Most of the results were consistent with the across trials, especially for important AEs such as serious infections, thrombotic events, and malignant. New significant AEs were detected such as diverticulitis, myocardial infarction, and dysstasia. Time to AE onset of upadacitinib was also analyzed. Our research provided valuable evidence for further safety studies of upadacitinib.

## Data Availability

All data used in the study appear in the submitted article.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Yazheng Zhao and Qian Cheng contribute equally to this manuscript.

## Supplementary Materials

Disproportionality analysis and four statistical algorithms used for signal detection of upadacitinib. (*Supplementary Materials*)

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