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Unveiling the risk

A comprehensive analysis of drug-induced aphthous ulcers using real-world data from FAERS

Xuefeng Wang, MS[a], Yingxue Huang, MS[a], Yanbo Zhang, MS[a], Xue Li, BS[a], Liqin Yang, BS[a], Peng Wang, MS[a,*]

Abstract

Drug-induced aphthous ulcers have emerged as a significant concern in clinical practice; however, their epidemiological characteristics remain unclear. This study aimed to investigate the link between various medications and the occurrence of drug-induced aphthous ulcers using real-world data for a comprehensive analysis. We conducted an extensive analysis of adverse event reports from the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) from the third quarter of 2015 through the fourth quarter of 2024. By employing disproportionality analysis along with Bayesian confidence propagation neural network algorithms, we identified medications associated with aphthous ulcers, assessed their risk levels, and compared the time to onset for different drug categories. Additionally, univariate and multivariate logistic regression analyses were performed to explore independent risk factors (including demographic characteristics, clinical comorbidities, and drug exposure) for drug-induced aphthous ulcers. Our findings revealed that 426 medications were associated with the development of aphthous ulcers in the FAERS database. Disproportionality analysis identified 26 drugs with significant risk factors, with infliximab, methotrexate, everolimus, secukinumab, and palbociclib ranking among the top 5 drugs likely to induce aphthous ulcers. Logistic regression analyses confirmed that the top 5 drugs, along with 8 other medications, were independent risk factors for drug-induced aphthous ulcers. Age, sex, and multiple comorbidities were independent influencing factors. Additionally, the time-to-onset analysis indicated that most implicated drugs led to early failure. Identifying the risk factors associated with drug-induced aphthous ulcers underscores the need for a prevention-focused management strategy. Healthcare professionals must remain vigilant about the potential risks of specific medications in triggering aphthous ulcers and should proactively relay this information to patients. Increased awareness and continuous monitoring can significantly reduce the incidence of drug-related oral mucosal lesions.

Abbreviations: ADEs = adverse drug events, ADRs = adverse reactions, CI = confidence interval, DEMO = patient demographics and management information, EBGM = empirical Bayes geometric mean, FAERS = FDA Adverse Event Reporting System, ROR = reporting odds ratio, THER = drug treatment start and end dates, TTO = time-to-onset, WSP = Weibull shape parameter.

Keywords: drug-induced aphthous ulcers, FAERS, pharmacovigilance, post-marketing surveillance, signal detection, time-to-onset

1. Introduction

Aphthous ulcers are the most prevalent oral mucosal conditions encountered in clinical practice. They are characterized by recurrent, self-limiting episodes predominantly affecting non-keratinized oral mucosal surfaces, such as the buccal and labial mucosa. This condition primarily affects young adults, with a prevalence of up to 20%.[1] Lesions are commonly found on the tip of the tongue, inner surface of the lips, tongue margins, ventral tongue, and soft palate, and present as painful white ulcers surrounded by erythema. The duration of episodes can be prolonged with frequent recurrences and significant discomfort.[2] The etiology of aphthous ulcers is multifaceted and involves microbiological, immunological, environmental, and genetic factors. Research indicates that dysbiosis of the intestinal microbiota and immune system imbalances may contribute to ulcer development.[3] Stress has been identified as a significant trigger, although some studies have reported no direct correlation between stress levels and salivary biomarkers.[4] Smoking may also play a complex role; it may reduce the incidence of aphthous ulcers by promoting a keratinized layer that prevents antigen penetration, while its combustion products may lead to oral keratosis, providing a protective effect.[5] Genetic predisposition has also been suggested with evidence of familial patterns,

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The datasets generated during and/or analyzed during the current study are publicly available.

Ethics approval and consent to participate are not applicable for this study.

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[a] Department of Stomatology, The Affiliated Hospital of Chengde Medical University, Chengde, Hebei, China.

** Correspondence: Peng Wang, Department of Stomatology, The Affiliated Hospital of Chengde Medical University, Chengde 067000, Hebei, China (e-mail: 15633142878@163.com).*

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although the underlying genetic mechanisms remain unclear.[6] Furthermore, aphthous ulcers can be associated with other health conditions, such as inflammatory bowel disease, potentially arising from a combination of gut microbiota dysbiosis and oral microtrauma.[7]

In some instances, medications can induce aphthous ulcers. Drugs, such as ibuprofen and tocilizumab, have been linked to the development of aphthous ulcers development.[8,9] Nicorandil, which is used for angina prevention, has recently been reported to cause both oral and genital ulcers.[10] In addition, etoricoxib causes erosive or aphthous-like lesions in the oral cavity.[11] Consequently, healthcare providers must remain vigilant regarding potential oral adverse reactions (ADRs) to these medications and may recommend discontinuation if necessary.

The objective of this study is to assess drug-induced aphthous ulcers using extensive real-world data from the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database.[12,13] To the best of our knowledge, there is currently no standardized consensus regarding drug-induced aphthous ulcers. Our research aimed to provide validation based on large sample data, contributing to the establishment of a consensus on this issue. Additionally, we highlight the potential risks posed by the drugs identified in this analysis that may induce aphthous ulcers. Ultimately, our goal was to determine which medications are associated with drug-induced aphthous ulcers in clinical settings and to evaluate their specific risk levels and timelines for onset. Effective assessment of the risk of drug-related ADRs facilitates accurate classification of aphthous ulcer subtypes, enabling timely and appropriate interventions.

2. Methods

2.1. Data source

Data for this study were sourced from the FAERS database, covering the period from January 1, 2004 to December 31, 2024. These data can be accessed on the Food and Drug Administration website (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). The FAERS database contains reports of spontaneous adverse events (ADEs) submitted by healthcare professionals, drug manufacturers, and users worldwide. It comprises 7 primary datasets: Patient demographics and management information (DEMO), drug and bioinformatics, adverse events (REACs), patient outcomes, source of report, drug treatment start and end dates (THER), and indications for drug use and diagnosis. To ensure data credibility, we focused on reports submitted by qualified healthcare professionals, particularly physicians and pharmacists (MDs and PHs). This approach facilitated a thorough analysis of the incidence of ADEs related to all drugs in the database as well as the epidemiological profile of drug-induced aphthous ulcers. For this analysis, we focused on reports on drug-induced aphthous ulcers. Based on our data exploration, cases specifically coded for aphthous ulcers were recorded in the database starting in the third quarter of 2015. Therefore, the effective analysis period for the target event (aphthous ulcer) spans the third quarter of 2015 to the fourth quarter of 2024. From this time window, we identified 6603 relevant adverse event reports for inclusion in the study.

2.2. Identification of adverse reactions

The definitions of ADEs analyzed in this study were based on the Medical Dictionary for Regulatory Activities (MedDRA, http://www.meddra.org/) version 20.0. ADEs were coded according to MedDRA-preferred terms, and a standardized MedDRA query was used to identify preferred terms associated with aphthous ulcers. In this study, the PT code designated for aphthous ulcers was 10002959.

2.3. Time-to-onset

Time-to-onset (TTO) was defined as the interval between the initiation date of suspected drug therapy (START_DT in the THER file) and the date of onset of adverse events (EVENT_DT in the DEMO file).[14] To ensure the integrity of the analysis, reports containing erroneous data entries, such as those where the event date preceded the start date or those with incomplete or missing dates, were excluded. Statistical measures, including medians, quartiles, and the Weibull Shape Parameter (WSP) test, were employed to evaluate the TTO in this study.[15,16]

The WSP test was used to analyze the temporal pattern of ADE incidence. The Weibull distribution is represented by 2 parameters: the scale parameter (α), which indicates the time scale for events to occur, and the shape parameter (β), which describes the nature of the failure rate over time. Specifically, a shape parameter $\beta > 1$ indicates an increasing failure rate, $\beta < 1$ indicates a decreasing rate, and $\beta = 1$ signifies a constant failure rate. We computed the median TTO and the corresponding WSP for signals with different levels of clinical significance. All WSP tests were conducted using R software (version 4.3.3) and the fitdistrplus package.

2.4. Statistical analysis

The signal detection in this study employed disproportionality analysis utilizing both frequency and Bayesian methods. Frequency methods include the reporting odds ratio (ROR) and proportional reporting ratio (PRR), whereas Bayesian methods involve the Bayesian confidence propagation neural network (BCPNN) and empirical Bayesian geometric mean (EBGM).[17–20] All 4 methods use a quadruple table calculation, as outlined in Table S1 (Supplemental Digital Content, https://links.lww.com/MD/R466). Potential positive signals were identified by comparing the target event and the corresponding drug against all other events and drugs. In the context of the described disproportionality analysis, "a" represents the occurrence frequency of target ADEs related to the drug in question. A drug was selected as a positive signal if it met the criteria outlined by the aforementioned 4 methods, indicating a potential association with the event. A detailed method for identifying positive signals is presented in Table S2 (Supplemental Digital Content, https://links.lww.com/MD/R466). ADEs were considered positive signals associated with aphthous ulcers only if their statistical correlation with the drug met the specified criteria and if they were reported with a frequency of 3 or more instances.

Univariate and multivariate binary logistic regression analyses were conducted to identify related and independent factors influencing the study outcome, specifically the drug-induced occurrence of aphthous ulcers. Continuous variables were reported as medians with interquartile ranges (Q1 and Q3), while categorical variables were presented as frequencies and percentages (n, percent). The baseline characteristics were compared between the outcome-positive and outcome-negative groups. Initially, all demographic characteristics, clinical comorbidities, and drug exposure factors were included in the univariate logistic regression analysis to calculate odds ratios and 95% confidence intervals (95% CIs). Variables demonstrating statistically significant differences ($P < .05$) in the univariate analysis were subsequently included in the multivariate logistic regression model to adjust for confounding effects, thereby identifying the independent factors influencing the study outcome. All statistical tests were two-tailed, and a P-value of <.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of subjects

From the third quarter of 2015 to the fourth quarter of 2024, 6603 ADEs classified as aphthous ulcers were identified in

the FAERS database. Since the initiation of data collection, reports on drug-induced aphthous ulcers have shown a general upward trend, culminating in a peak in 2024 (Fig. 1A). Excluding cases with missing data, patients aged 60 years and older constituted the largest group, accounting for 27.3% of reports (Fig. 1B). Additionally, the majority of cases involved patients weighing 50 to 100 kg, accounting for 25.5% of cases (Fig. 1C). Sex analysis indicated that women were more frequently affected, accounting for 58.7% of cases (Fig. 1D). Among the reported ADRs, 26.4% involved hospitalization (Fig. 1E). The United States reported the highest number of drug-induced aphthous ulcer cases, accounting for 32.3% of all the reports (Fig. 1F).

3.2. Risk values of drugs associated with drug-induced aphthous ulcers

The top 30 drugs associated with drug-induced aphthous ulcers are presented in Figure 2, which also details the metrics ROR, PPR, BCPNN, and EBGM. The risk rankings of the drugs varied depending on the disproportionality metric. The 3 drugs with the highest absolute numbers of reports were infliximab (1112 cases), methotrexate (314 cases), and everolimus (223 cases). However, when ranked by the strength of the ROR and PPR, the top drugs differed; sodium fluoride, stannous fluoride, and polyethylene glycol showed the strongest signals using both the ROR and proportional reporting ratio methods. The BCPNN statistics ranked infliximab, everolimus, and sodium fluoride as the top 3. Based on the primary EBGM metrics, the highest-ranking drugs were sodium fluoride, stannous fluoride, and polyethylene glycol.

3.2.1. Age-based analysis. Age ranking analysis showed that infliximab was most frequently associated with drug-induced aphthous ulcers in individuals aged 19 to 44 and 44 to 59 years. For patients younger than 19 years, everolimus had the highest incidence of drug-induced aphthous ulcers. In contrast, methotrexate was the most common cause among individuals aged 60 years and older, as illustrated in Figure 3.

3.2.2. Gender-based analysis. In both women and men, the 3 drugs most commonly associated with drug-induced aphthous ulcers were infliximab, methotrexate, and everolimus. In analyses based on ROR, PPR, and EBGM, infliximab consistently recorded the highest scores for both genders, with further details provided in Figure 4.

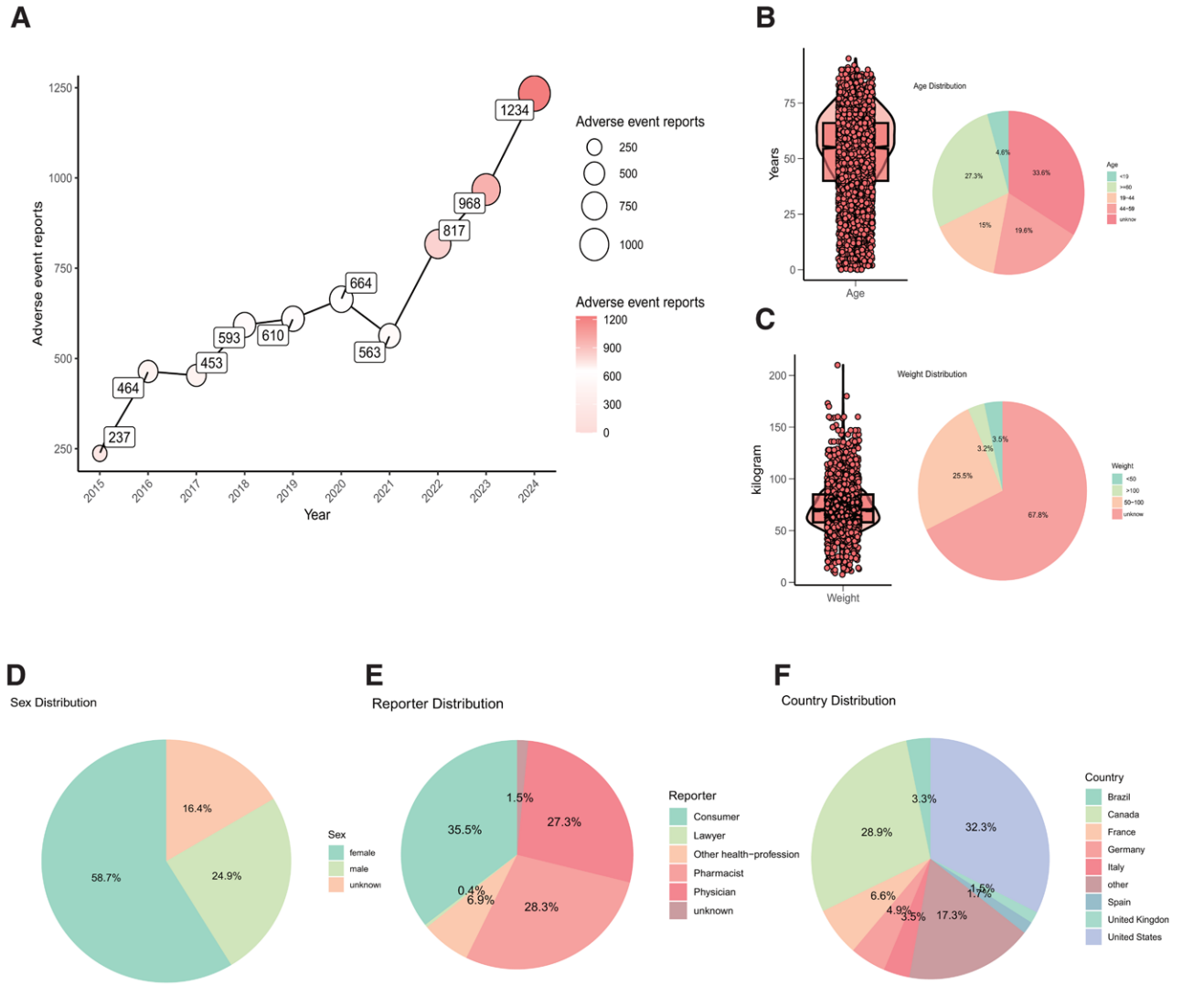

Figure 1. Reporting characteristics associated with drug-induced aphthous ulcer from Q3 2015 to Q4. (A) Annual trend of adverse event reports (2015–2024); (B) Age distribution of patients with adverse events; (C) Weight distribution of patients with adverse events; (D) Sex distribution of patients with adverse events; (E) Reporter distribution of adverse events; and (F) Country distribution of adverse event reports.

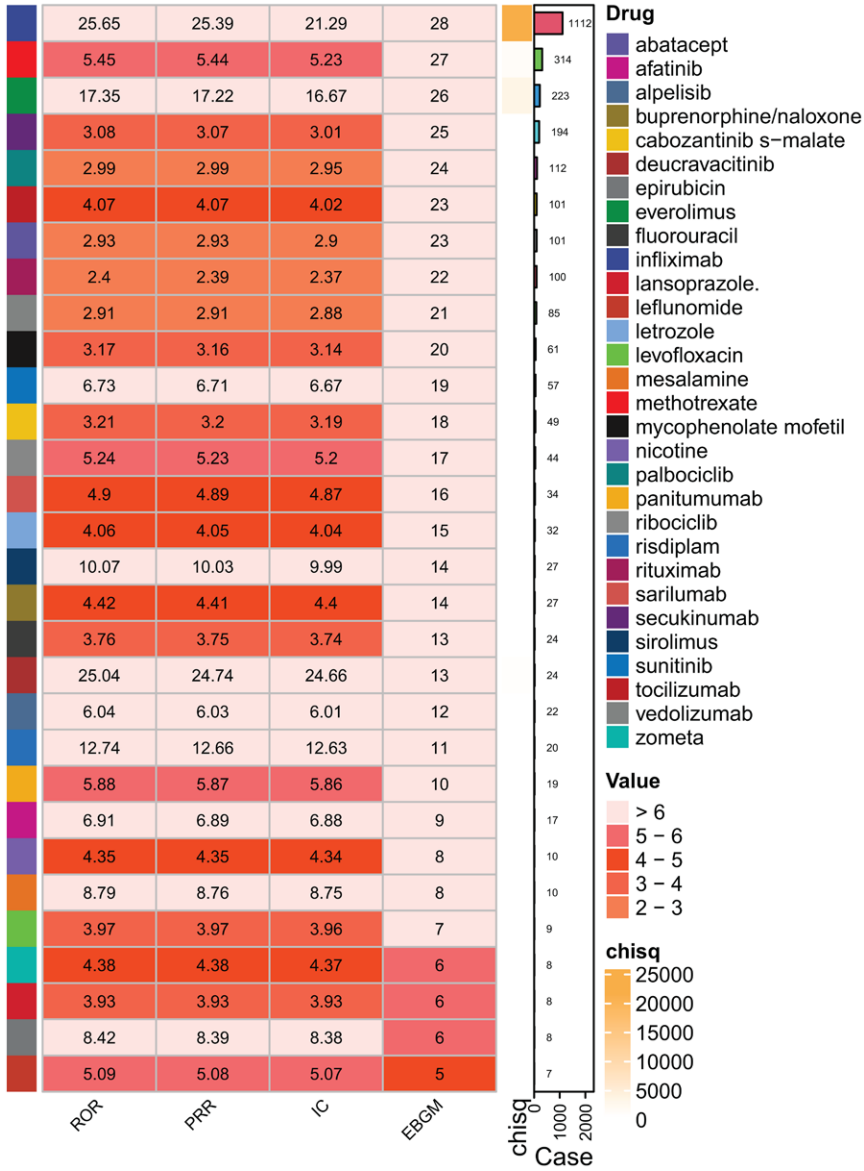

Figure 2. Top 30 risk signals for the number of reported ADRs associated with drug-induced aphthous ulcer. ADRs = adverse reactions.

3.3. Time-to-onset analysis

To assess the temporal risk associated with these drugs, we calculated the median TTO and WSP of drugs that could potentially lead to drug-induced aphthous ulcers. Excluding cases that were unreported or had fewer than 20 occurrences, the results of the analysis are summarized in Figure 5. The median onset time for patients classified as having moderate signals was within 15 days (Fig. 5A). The pie chart shows the proportion of cases with different onset time intervals: 58.4% cases have unknown onset time, 11.0% cases have onset within 1 to 15 days after medication, and 9.6% cases have onset time <1 day, suggesting that most drug-related oral ulcers are characterized by "early onset" (Fig. 5B). Furthermore, in the WSP analysis, all shape parameters (β), along with their corresponding upper limits of the 95% CI, were <1, indicating that these moderately clinically relevant signals follow an early failure pattern (Fig. 5C).

3.4. Baseline characteristics of the study population and intergroup comparison

A total of 1,750,431 participants were included in this study, comprising 1759 individuals (0.10%) with positive study outcomes (aphthous ulcers) and 1,748,672 individuals (99.90%) with adverse study outcomes (Table S3, Supplemental Digital Content, https://links.lww.com/MD/R466). Baseline comparisons revealed statistically significant differences in demographic characteristics, including age, sex, and body weight, between the 2 groups ($P < .001$). The median age of the positive outcome group was lower [55 years (interquartile range: 37, 66) compared to 60 years (interquartile range: 43, 71)], the proportion of females was higher in the positive outcome group (71.69% compared to 59.65%), and the median body weight was lower in the positive outcome group [70 kg (interquartile range: 58, 85) compared to 72.50 kg (interquartile range: 59.42, 87.98)].

When examining clinical comorbidities, significant intergroup differences were identified in the prevalence of hypertension, myeloma, diabetes mellitus (DM), breast cancer, Crohn disease, pulmonary arterial hypertension, atrial fibrillation, psoriasis, chronic obstructive pulmonary disease (COPD), and constipation, with all differences reaching statistical significance ($P < .05$). Conversely, no significant differences were observed in the prevalence of gastroesophageal reflux disease, pain, depression, asthma, anxiety, psoriatic arthropathy, or multiple sclerosis (all $P > .05$). The aphthous ulcer group exhibited significantly lower proportions of patients with hypertension,

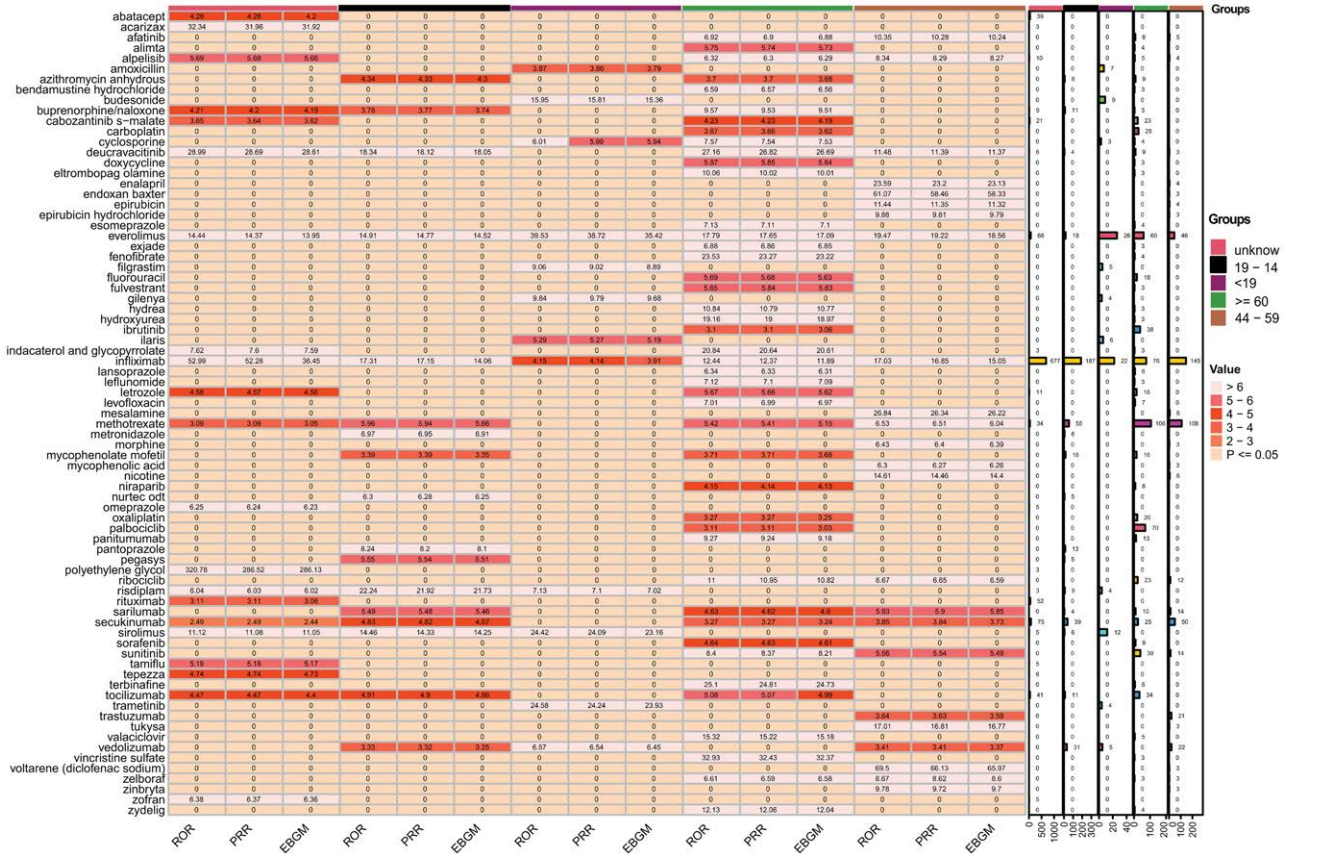

Figure 3. Risk signals by age in the number of drug-induced aphthous ulcer related ADRs reports. ADRs = adverse reactions.

myeloma, DM, pulmonary arterial hypertension, atrial fibrillation, and COPD pulmonary disease than the negative group, whereas the proportions of patients with breast cancer and Crohn disease were significantly higher. Regarding drug exposure factors, significant differences were found in the exposure rates to infliximab, methotrexate, everolimus, secukinumab, palbociclib, tocilizumab, vedolizumab, mycophenolate mofetil, sunitinib malate, cabozantinib S-malate, ribociclib, letrozole, and contraception between the 2 groups (all $P < .05$). However, no significant differences were detected in the exposure rates to abatacept, rituximab, or sarilumab (all $P > .05$). The exposure rates to the above drugs, with statistically significant differences in the aphthous ulcer group, were significantly higher than those in the negative group.

3.5. Results of univariate logistic regression analysis

Univariate logistic regression analysis was conducted, incorporating all variables, including demographic characteristics, clinical comorbidities, and drug exposure factors (Table S4, Supplemental Digital Content, https://links.lww.com/MD/R466). The analysis revealed significant associations between study outcomes and age (OR = 0.991, 95% CI: 0.989–0.993, $P < .001$), sex (OR = 0.584, 95% CI: 0.526–0.648, $P < .001$), and body weight (OR = 0.996; 95% CI: 0.994–0.998, $P < .001$). Among the clinical comorbidities, significant correlations were identified for hypertension (OR = 0.272, 95% CI: 0.179–0.415, $P < .001$), myeloma (OR = 0.271, 95% CI: 0.154–0.478, $P < .001$), DM (OR = 0.163, 95% CI: 0.081–0.326, $P < .001$), breast cancer (OR = 2.101, 95% CI: 1.712–2.579, $P < .001$), Crohndisease (OR = 7.630, 95% CI: 6.534–8.910, $P < .001$), pulmonary arterial hypertension (OR = 0.142, 95% CI: 0.053–0.379, $P < .001$), atrial fibrillation (OR = 0.066, 95% CI: 0.009–0.469, $P = .007$), contraception (OR = 0.197, 95% CI: 0.099–0.394, $P < .001$),psoriasis (OR = 0.473, 95% CI: 0.261–0.855, $P = .013$), and COPD (OR = 0.232, 95% CI: 0.058–0.927, $P = .039$), with all associations achieving statistical significance ($P < .05$).

Among the factors related to drug exposure, significant associations with the study outcome were observed for infliximab (OR = 13.563, 95% CI: 12.048–15.270, $P < .001$), methotrexate (OR = 7.242, 95% CI: 5.880–8.921, $P < .001$), everolimus (OR = 16.280, 95% CI: 12.262–21.613, $P < .001$), secukinumab (OR = 3.826, 95% CI: 2.665–5.493, $P < .001$), palbociclib (OR = 2.093, 95% CI: 1.440–3.041, $P < .001$), tocilizumab (OR = 4.511, 95% CI: 3.268–6.225, $P < .001$), vedolizumab (OR = 3.092, 95% CI: 1.790–5.340, $P < .001$), mycophenolate mofetil (OR = 2.460, 95% CI: 1.102–5.488, $P = .028$), sunitinib malate (OR = 8.560, 95% CI: 5.992–12.229, $P < .001$), cabozantinib S-malate (OR = 4.221, 95% CI: 2.190–8.137, $P < .001$), ribociclib (OR = 9.903, 95% CI: 6.427–15.259, $P < .001$),and letrozole (OR = 2.975, 95% CI: 1.544–5.732, $P = .001$), withall P-values being <.05. Conversely, no significant associations were identified between the study outcomes and the use of abatacept, rituximab, or sarilumab, as indicated by P-values > .05.

3.6. Results of multivariate logistic regression analysis

After controlling for confounding variables, age (OR = 0.997, 95% CI: 0.994–0.999, $P = .004$) and sex (OR = 0.583, 95% CI: 0.524–0.649, $P < .001$) emerged as independent determinants of study outcome (Table S4, Supplemental Digital Content, https://links.lww.com/MD/R466). Among the clinical comorbidities examined, hypertension (OR = 0.459, 95% CI: 0.288–0.732, $P = .001$), myeloma (OR = 0.425, 95% CI: 0.240–0.752,

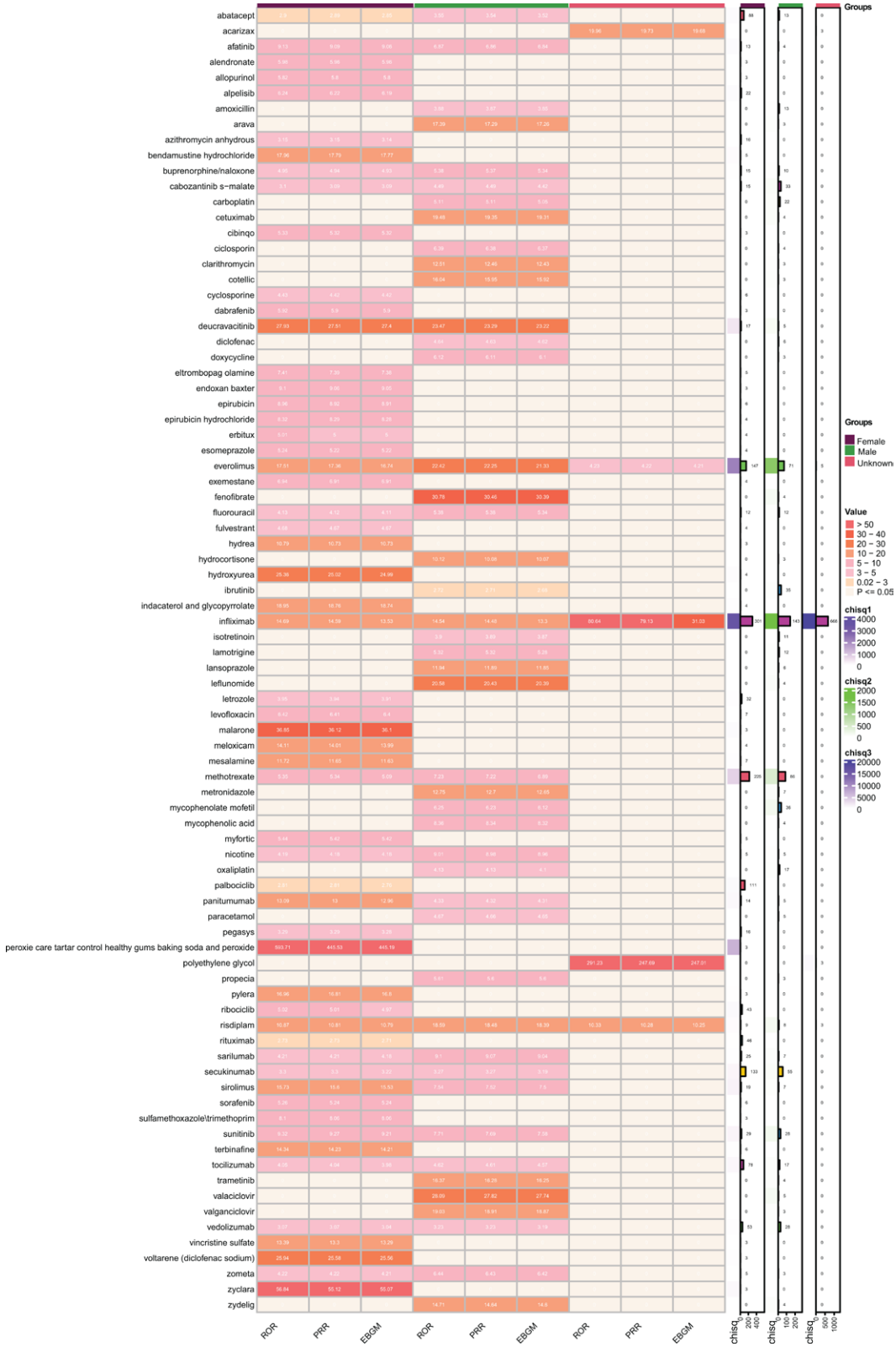

Figure 4. Risk signals by gender in the number of drug-induced aphthous ulcer related ADRs reports. ADRs = adverse reactions.

P = .003), DM (OR = 0.234, 95% CI: 0.117–0.469, *P* < .001), Crohn disease (OR = 1.410, 95% CI: 1.162–1.710, *P* < .001), atrialfibrillation (OR = 0.107, 95% CI: 0.015–0.754, *P* = .025), Contraception (OR = 0.207, 95% CI: 0.103–0.417, *P* < .001) and psoriasis (OR = 0.312, 95% CI: 0.170–0.575, *P* < .001) were also identified as independent influencing factors, with all *P*-values being <.05.

In this study, contraception and all included drug exposure factors were identified as independent risk factors for the outcome (Table S4, Supplemental Digital Content,

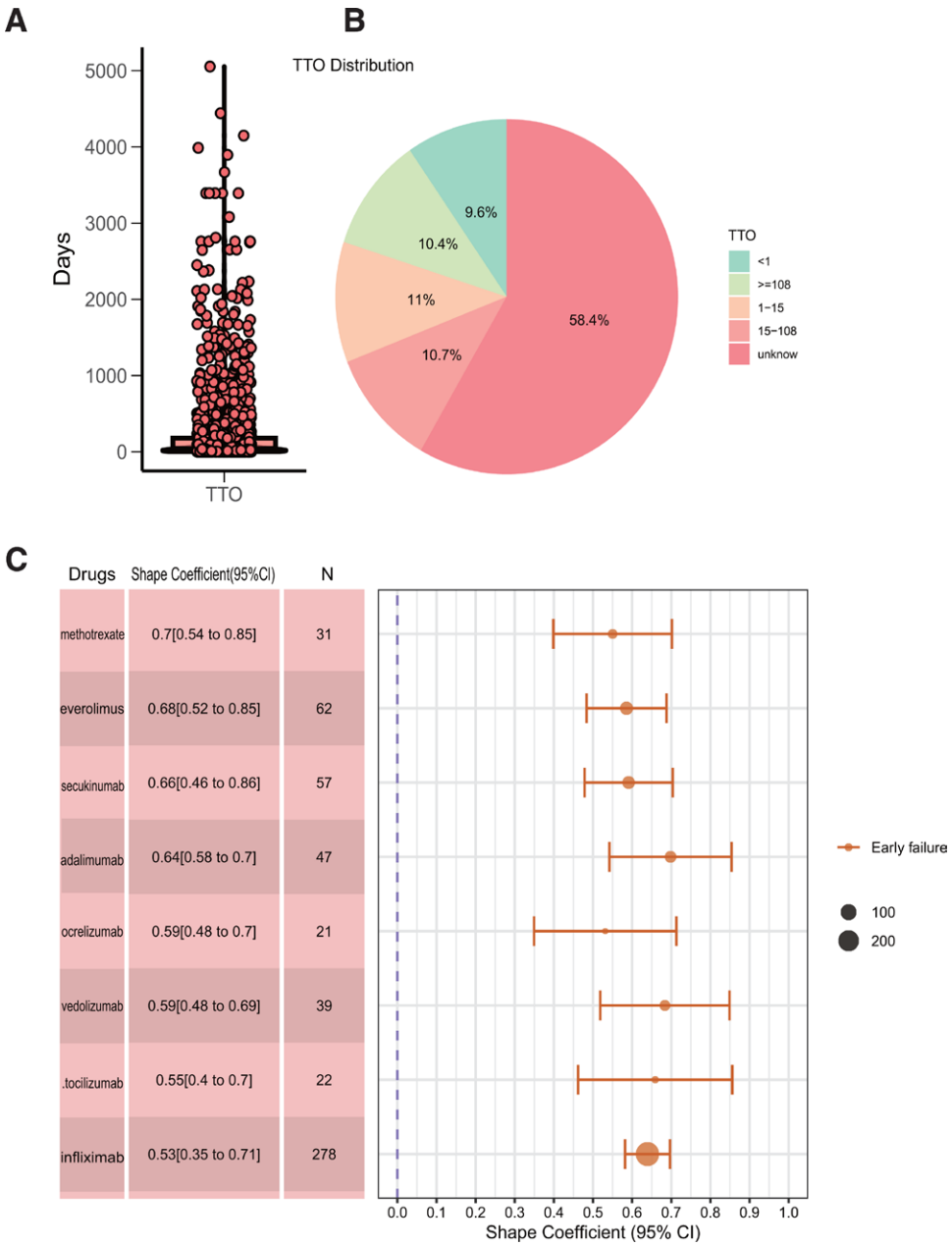

Figure 5. Time-to-onset analysis for the signals of drug-induced aphthous ulcer. (A) Scatter plot of TTO for drug-induced aphthous ulcers; (B) Composition of TTO intervals; (C) Shape coefficient of early failure risk for high-risk drugs. TTO = time-to-onset.

https://links.lww.com/MD/R466), and statistical significance was observed for all factors (all $P < .05$). After adjustment, the risk effects associated with most drugs were amplified. The specific results are as follows: infliximab (OR = 13.057, 95% CI: 11.209–15.211, $P < .001$), methotrexate (OR = 9.329, 95% CI: 7.542–11.540, $P < .001$), everolimus (OR = 20.563, 95% CI: 15.276–27.680, $P < .001$), secukinumab (OR = 6.962, 95% CI: 4.785–10.129, $P < .001$), palbociclib (OR = 2.113, 95% CI: 1.375–3.249, $P = .001$), tocilizumab (OR = 5.831, 95% CI: 4.213–8.070, $P < .001$), vedolizumab (OR = 3.641, 95% CI: 2.091–6.340, $P < .001$), mycophenolate mofetil (OR = 3.417, 95% CI: 1.529–7.635, $P = .003$), sunitinib malate (OR = 14.061, 95% CI: 9.806–20.164, $P < .001$), cabozantinib S-malate (OR = 7.125, 95% CI: 3.687–13.767, $P < .001$), ribociclib (OR = 10.129, 95% CI: 6.346–16.167, $P < .001$), and letrozole (OR = 3.161, 95% CI: 1.613–6.196, $P = .001$).

4. Discussion

This study analyzed ADRs associated with drug-induced aphthous ulcers using data from the FAERS database from the third quarter of 2015. To the best of our knowledge, this is the first investigation of drug-induced aphthous ulcers in the FAERS database that has been validated using actual patient data. Current research on the mechanisms underlying drug-induced aphthous ulcers is limited. Our findings provide both data support and a theoretical framework for reducing ADRs and guiding the rational use of medications in clinical settings.

Logistic regression analysis revealed that age and sex were linked to the development of drug-induced aphthous ulcers, which are oral ulcers caused by certain medications. Women, in particular, seem to be more susceptible to drug reactions. For example, a case report documented a female adolescent developing aphthous ulcers from high-dose bupropion for depression, with symptoms recurring upon rechallenge, indicating a higher

risk of depression in women.[8] Studies have shown sex differences in drug-induced esophageal ulcers, with women accounting for 70.9% of cases, highlighting their higher risk.[21] Age also plays a role, as young and middle-aged women often face serum ferritin deficiency, whereas young men are more prone to folic acid and vitamin B12 deficiencies, both of which are associated with recurrent aphthous ulcers.[22] Thus, age and sex may affect ulcer development. The findings of this study further indicate that pathogenic factors contributing to drug-induced aphthous ulcers are associated with various diseases, including hypertension, myeloma, DM, Crohn disease, atrial fibrillation, contraception, and psoriasis. Numerous studies have investigated the correlation between aphthous ulcers and systemic diseases. For instance, a meta-analysis demonstrated that deficiencies in blood indices such as vitamin B12, folic acid, and ferritin are significantly linked to aphthous ulcers, suggesting that metabolic disorders may play a role in their pathogenesis.[23] Furthermore, aphthous ulcers are associated with inflammatory bowel diseases, such as Crohn disease, reinforcing the hypothesis that systemic inflammation and immune dysregulation may contribute to the development of these ulcers.[24] A case of inflammatory bowel disease induced by secukinumab, in which recurrent oral ulcers preceded ileitis and pancolitis, illustrates the potential utility of aphthous ulcers as early indicators of systemic inflammatory diseases.[9] Furthermore, a retrospective cohort study found that individuals with cardiovascular disease or metabolic risk factors exhibited a higher propensity for ulcer recurrence, indicating a potential link between cardiovascular health and aphthous ulcers.[25] This association is corroborated by additional observations that revealed that patients with aphthous ulcers have an elevated risk of developing autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, which are frequently comorbid with cardiovascular diseases.[26] These findings underscore the intricate interplay between systemic diseases and aphthous ulcers, highlighting the need for holistic consideration of the patients' overall health status in the diagnosis and management of these ulcers.

In the present study, the drugs most likely to cause aphthous ulcers were infliximab, methotrexate, everolimus, secukinumab, and palbociclib. Infliximab, a TNF-α inhibitor, is effective in managing autoimmune conditions such as Crohn disease and ulcerative colitis but may also induce aphthous ulcers in some patients. This effect is particularly notable in patients treated for ulcerative colitis, potentially due to the exacerbation of mucosal lesions resulting from immunomodulation.[27] Methotrexate, a disease-modifying antirheumatic drug, has been reported to cause mucosal damage that can lead to aphthous ulcers, primarily because its mechanism of action involves the inhibition of folate metabolism, an essential pathway for mucosal cell proliferation.[28] Everolimus, an mTOR inhibitor used in organ transplantation and certain cancers, has been linked to mouth ulcers, especially in transplant recipients, because of its immunosuppressive properties, which may compromise mucosal integrity.[29] Secukinumab, an IL-17A inhibitor for conditions such as psoriasis and psoriatic arthritis, has been associated with inflammatory bowel disease manifesting as oral aphthous ulcers, suggesting a possible connection between IL-17A inhibition and mucosal ulceration.[9] Lastly, palbociclib, a CDK4/6 inhibitor primarily used for breast cancer, although mainly linked to haematotoxicity as a side effect, has also been noted to cause oral ulcers, likely because of its impact on rapidly dividing mucosal cells during cell cycle inhibition.[30] These findings corroborate our analysis.

Our study also observed that the incidence of drug-induced aphthous ulcers was higher in individuals aged > 60 years and was more prevalent among women. Some studies have indicated that the occurrence of aphthous ulcers correlates with age. For instance, one study examining hemoglobin deficiency in patients with aphthous ulcers revealed significant differences in the levels of ferritin, folate, and vitamin B12 deficiencies across different age groups. Notably, ferritin deficiency is particularly common among middle-aged women and potentially contributes to the development of aphthous ulcers.[22] Moreover, with aging, the immune system undergoes changes that can affect the body's response to infection and inflammation. Research suggests that older adults may experience alterations in both humoral and cellular immunity, which may influence the pathogenesis of aphthous ulcers. One study investigating immune-related gene expression in aphthous ulcers revealed a predominant association with Th1-type immune responses that may be affected by hormonal fluctuations across sexes.[31] Another study indicated that women with aphthous ulcers are at an increased risk of developing autoimmune diseases.[26] This suggests a potential connection between sex, age, and the occurrence of aphthous ulcers.

The median onset time for stomatitis induced by high-risk drugs, such as infliximab, methotrexate, everolimus, and secukinumab, is 15 days after treatment initiation, which is clinically significant. These oral ulcers can degrade the patients' quality of life and may necessitate changes in treatment. Understanding the onset and risk factors is crucial for effective management. Research on high-dose MTX-induced stomatitis, linked to factors such as rash, fever, neutropenia, acute kidney injury, and delayed drug clearance, offers insights that may be applicable to other drugs causing oral ulcers.[32] The onset of these ulcers can be influenced by various factors including drug dosage and patient immunity. Clinicians should enhance the monitoring of oral mucosal symptoms within 2 to 4 weeks of starting high-risk drugs such as infliximab, everolimus, and methotrexate. Routine oral examinations should be conducted at the initial follow-up, and patients should be informed of typical aphthous ulcer symptoms, such as painful oral ulcers, erythema, and mucosal erosion. Patients should promptly report any oral symptoms for early diagnosis and intervention, which may include dosage adjustment, use of local analgesics or anti-inflammatory drugs, or discontinuation of the drug in severe cases. These steps are crucial to reduce the burden of aphthous ulcers and improve patient compliance.

This study has several limitations that warrant recognition. First, although disproportionate analysis can be used to assess the association between targeted drugs and ADEs, it does not establish a definitive causal relationship. Second, although subgroup analyses were performed based on age, sex, country, and disease, the data sourced from the FAERS database depended on voluntary and spontaneous reporting, which may have been influenced by recent studies or media coverage, potentially introducing bias. Finally, the FAERS database is an open self-reporting system, resulting in non-standardized data quality due to variability among report submitters, which can lead to skewed results.

5. Conclusion

Although a clear causal relationship between a specific drug and aphthous ulcers cannot be directly established through statistical means, this study effectively employed a systematic approach to identify potential drug-related triggers of aphthous ulcers using a comprehensive, real-world adverse drug reaction database. By analyzing individual risk factors, dose correlations, and time trajectories concerning the onset of oral ulcers across various drug classes, we revealed the distinct characteristics and effects associated with drug-induced aphthous ulcers. In particular, this study highlights that medications such as infliximab, methotrexate, everolimus, secukinumab, and palbociclib predispose patients to drug-induced aphthous ulcers. These findings contribute significantly to our understanding of the epidemiological characteristics of drug-induced aphthous ulcers and provide valuable data-driven insights that can inform clinical

practices aimed at reducing their incidence. By outlining the associated risk profiles, patterns of pathogenesis, and potential strategies to mitigate drug-induced aphthous ulcers, this study lays a solid foundation for clinical decision-making and enhanced patient care. These data can guide healthcare professionals in recognizing at-risk populations, implementing preventive measures, and making informed choices regarding the management of patients who may be vulnerable to ADRs. Ultimately, this study underscores the importance of ongoing surveillance and analysis of drug-related ADEs to enable improved patient outcomes and foster safer therapeutic practices.

Author contributions

Data curation: Xue Li.
Formal analysis: Yingxue Huang.
Software: Yanbo Zhang.
Supervision: Liqin Yang.
Writing – original draft: Xuefeng Wang.
Writing – review & editing: Peng Wang.

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