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Article

Adverse event reporting of golimumab: A disproportionality analysis of the FDA adverse event reporting system (FAERS) database

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ABSTRACT

This study conducted a retrospective disproportionality analysis of 50,031 adverse drug events (ADEs) reports from the FDA Adverse Event Reporting System (FAERS) database spanning Q2 2009 to Q3 2025, in which golimumab was identified as the primary suspect drug. Four disproportionality algorithms were simultaneously applied: the reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS). A total of 397 positive

signals were identified across 25 system organ classes (SOCs). The SOCs with concordant positive signals across all four algorithms were identified for infections and infestations and surgical and medical procedures. High-frequency signals included pneumonia, lower respiratory tract infection, influenza, nasopharyngitis, sinusitis and cellulitis. Comparison with the current prescribing information revealed several previously undocumented ADEs, including urinary tract infection, ear infection, flavivirus infection, Zika virus infection and Dengue fever. Twenty-nine positive malignancy signals absent from the prescribing information were identified, including basal cell carcinoma, colorectal cancer, cervical cancer and breast cancer. Time-to-onset analysis revealed that the risk of ADEs was the highest within the first few months of treatment initiation. Clinicians should rigorously monitor for infectious complications and malignancies when prescribing golimumab to ensure patient safety.

Keywords: golimumab, FAERS, ADE, signal mining

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INTRODUCTION

Tumor necrosis factor-alpha (TNF-α) inhibitors are a class of biologic agents used in the treatment of various immune-mediated inflammatory diseases, exerting their therapeutic effects by blocking TNF-α activity and downregulating downstream inflammatory signaling pathways (1). Golimumab is a fully human anti-TNF-α monoclonal antibody that specifically binds to both soluble and transmembrane biologically active forms of TNF-α, forming a complex that blocks the binding of TNF-α to its receptor and thereby inhibits the biological activity of TNF-α (2). It is currently approved primarily for the treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS) (3).

Golimumab received its initial marketing authorization from the United States Food and Drug Administration (FDA) in 2009, followed by approval from the European Medicines Agency (EMA) in the same year, and entered the Chinese market in 2018 (4). Prior to approval, the FDA incorporated black box warnings for serious infections and malignancies into the drug's prescribing information; these warnings have been revised on subsequent occasions, though the scope of updates may not fully reflect all known risks, and the safety profile of golimumab warrants continued attention. Multiple clinical trials conducted both within China and internationally have evaluated the safety of golimumab in RA and AS, identifying numerous adverse drug events (ADEs) that were undetected during pre-approval studies (5–7). Among these, serious adverse events (SAEs) accounted for a certain proportion, and fatal cases

have been reported (8). These findings not only reveal the limitations of pre-marketing safety evaluation but also highlight the necessity of conducting post-marketing surveillance based on real-world data. The FDA Adverse Event Reporting System (FAERS), as the world's largest spontaneous adverse event reporting database, has been widely used in post-marketing drug safety surveillance and can provide valuable real-world evidence to support clinical decision-making.

This study is the first to draw on the FAERS database and jointly apply four pharmacovigilance disproportionality analysis algorithms, namely reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS), to systematically evaluate the real-world safety profile of golimumab, thereby providing clinicians with more reliable evidence-based data for appropriate drug selection and prevention of adverse drug events (9).

MATERIALS AND METHODS

Data source and pre-processing

This retrospective analysis draws on quarterly raw data extracted from the FAERS database (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). The FAERS dataset comprises seven sections: DEMO (patient demographic and administrative information), DRUG (drug-specific details), REAC (coded adverse events), OUTC (patient outcomes), RPSR (report sources), THER (therapy initiation and cessation dates), and INDI (indications for drug use). Reported drugs in FAERS are categorized into four groups: PS (primary suspect), SS (secondary suspect), C (concomitant), and I (interacting) (9). To ensure comprehensive retrieval, both brand names and generic names for golimumab preparations were used as search terms, including “Simponi," "golimumab," and "Simponi Aria." The query covered reports from the second quarter of 2009 through the third quarter of 2025, and only records in which golimumab was designated as the primary suspect drug were included for analysis.

To address duplicate reports, we adopted the methodology recommended by the FDA. We selected the PRIMARYID, CASEID, and FDA_DT fields from the DEMO table and sorted them by CASEID, FDA_DT, and PRIMARYID. We retained the report with the largest FDA_DT value for cases with the same CASEID. Subsequently, for cases with both the same CASEID and FDA_DT, we kept the report with the largest PRIMARYID value. A list of

deleted reports was included in each quarterly data package since Q2 2009, and after data deduplication, reports were excluded based on the CASEID present in the list of deleted reports (10). All preferred terms (PTs) and system organ classes (SOCs) were coded and categorized using the medical dictionary for regulatory activities (MedDRA), version 28.0 (11).

Statistical analysis

Disproportionality analysis was employed to quantitatively evaluate golimumab-associated ADE signals. This analysis typically comprises two components: frequency-based statistics and Bayesian statistics. Frequency-based statistics includes the ROR and PRR, while Bayesian statistics encompasses the MGPS and BCPNN. Although the frequency-based ROR and PRR methods offer high sensitivity, computational simplicity, and earlier detection of certain signals, they are prone to false-positive signals when the number of events is small; therefore, their standalone application is susceptible to the masking effect (9). In contrast, BCPNN and MGPS demonstrate superior performance in detecting low-frequency events and can reduce false-positive signals compared with the frequency-based methods. The integrated use of all four methods leverages their complementary strengths and minimizes biases inherent to any single approach (10).

In this study, a signal was considered positive only when the positivity thresholds of all four algorithms were simultaneously met, indicating the generation of an ADE risk signal. The positivity criterion for ROR was defined as a 95 % confidence interval lower limit > 1 with at least three reports; for PRR, as PRR $\geqslant$ 2 with a $\geqslant$ 3 χ^2 value $\geqslant$ 4; for BCPNN, as IC025 > 0; and for MGPS, as EBGM05 > 2 (9). The 2×2 contingency table used in the descriptive analysis is presented in Table S1, and the specific formulas and positivity thresholds for all four algorithms are provided in Table S2.

Time to onset (TTO) was defined as the interval between the date of ADE occurrence (from the DEMO file) and the date of treatment initiation (from the THER file). Cases in which the ADE occurred before therapy initiation, as well as those with inaccurate or missing key information, were excluded. The Weibull distribution test was applied to evaluate the temporal trend of ADE incidence, allowing for the determination of whether the risk demonstrated an increasing or decreasing tendency (12). Data processing was conducted using MySQL; data visualization was performed using the "matplotlib" package in Python 3.6.

RESULTS AND DISCUSSION

Basic characteristics of ADE reports

As shown in Fig. 1, the flowchart illustrates the complete process of data extraction and analysis. The initial dataset comprised 21,757,413 records. After removing 3,498,215 duplicate entries, we obtained 18,259,198 unique demographic records (DEMO). Subsequently, after further filtering of drug records (DRUG) and adverse reaction records (REAC) associated with golimumab, a total of 50,031 reports of golimumab-induced adverse events were ultimately identified, involving 123,969 adverse event cases.

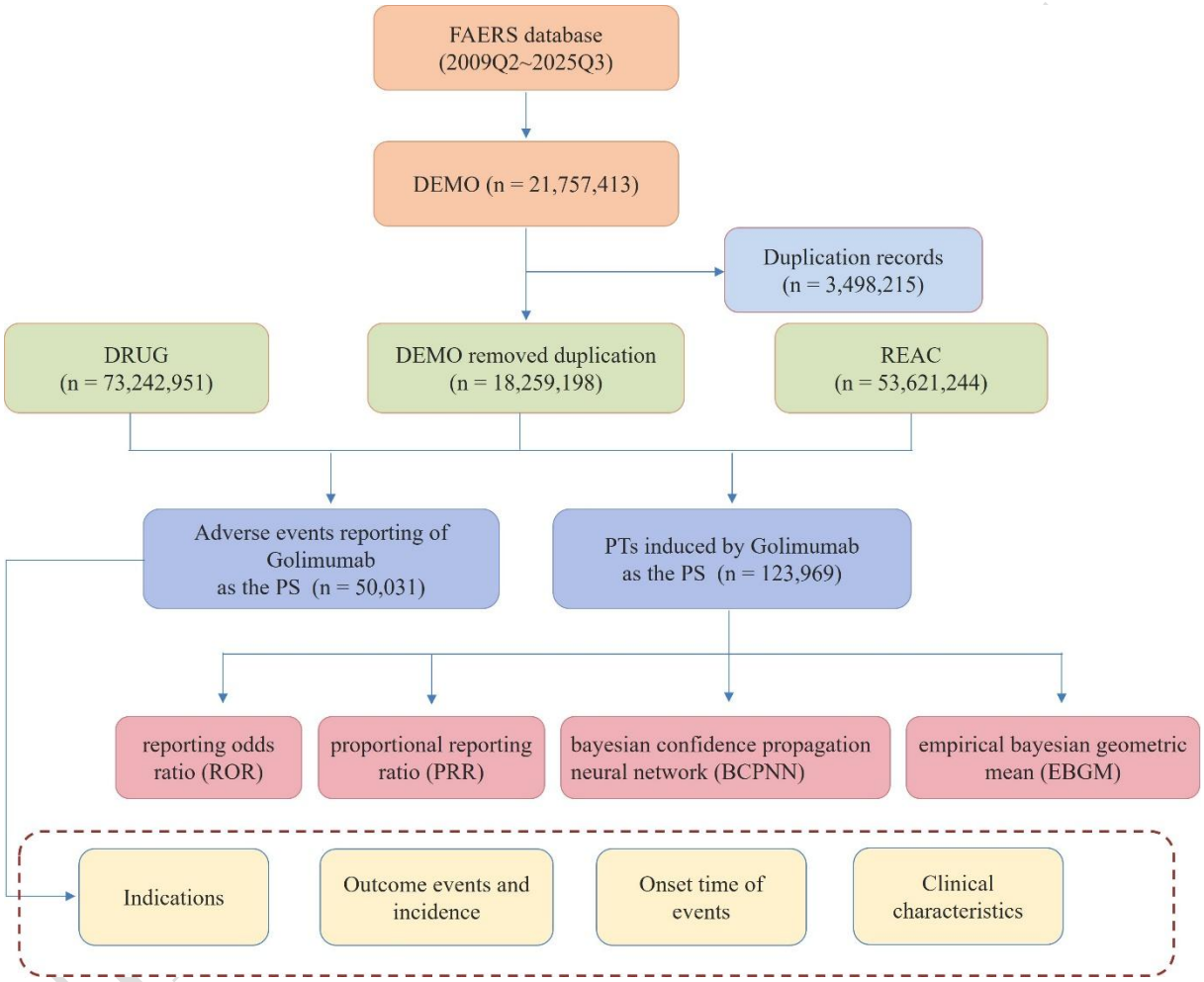


Fig. 1. Flowchart of the screening process for golimumab-related adverse drug events (ADEs).

From the second quarter of 2009 through the fourth quarter of 2015, the number of adverse event reports increased overall, peaking at 5,098 cases in 2015. After that, the number remained high, with annual totals exceeding 3,000 cases every year from 2016 to 2025 (Fig. S1). This reflects the widespread use of golimumab in real-world clinical practice. Demographic data are shown in Table I. Among reports with complete demographic data, the male-to-female ratio was 0.4:1, which may reflect a higher prevalence of the drug's indications in female patients

(13). The most frequent reporter occupations were nurses (21,953 reports, 43.9 %) and physicians (8,489 reports, 17.0 %). Approximately three-quarters of the reports were submitted by healthcare professionals, suggesting good reliability of the reported events. The most common reported outcomes were hospitalization or prolonged hospitalization (9,416 reports, 18.8 %) and other serious (important medical event) (21,477 reports, 42.9 %). The majority of reports originated from the United States (17,527 reports, 35.0 %), followed by Canada (7,844 reports, 15.7 %), the United Kingdom (4,886 reports, 9.8 %), and Brazil (4,371 reports, 8.7 %). The geographic distribution characteristics reported herein may be influenced by inter-regional differences in drug utilization and spontaneous reporting practices.

Table I. Demographic characteristics of ADEs reported in the FAERS database with golimumab as the primary suspect drug

Variable		Case numbers (*n*)	Percentage (%)
Sex	Male	13,087	26.2
	Female	31,948	63.9
	Unknown	4,996	10.0
Age (years)	≤ 17	254	0.5
	18–64	21,754	43.5
	65–85	9,352	18.7
	> 85	458	0.9
	Unknown	18,213	36.4
Reporter	Registered nurse	21,953	43.9
	Physician	8,489	17.0
	Pharmacist	5,455	10.9
	Lawyer	7	0.0_1
	Other health professional	7,387	14.8
	Unknown	6740	13.5
Outcomes	Death	1,136	2.3
	Disability	260	0.5
	Life-threatening	311	0.6
	Hospitalization	9,416	18.8
	Congenital anomaly	27	0.0_5
	Other serious	21,477	42.9
	Unknown	17,404	34.8
Reported countries (top five)	United States	17,527	35.0

	Canada	7,844	15.7
	United Kingdom	4,886	9.8
	Brazil	4,371	8.7
	Japan	2,921	5.8
	Other	12,482	25.0

Signal detection at the system organ class level

After excluding drug-unrelated MedDRA SOC categories (social circumstances and product issues), 25 SOCs remained, ranked by report frequency. The three most commonly affected SOCs were Infections and infestations (21.9 %), Injury, Poisoning and Procedural Complications (15.8 %), and General disorders and administration site conditions (14.9 %), as shown in Fig. S2. Positive signals meeting the criteria of all four algorithms were identified for Infections and infestations (ROR: 4.25 [4.19–4.31]; PRR: 3.63 [χ^2: 47,114]; EBGM05: 3.56; IC025: 1.83) and Surgical and medical procedures (ROR: 2.39 [2.31–2.46]; PRR: 2.34 [χ^2: 3,107]; EBGM05: 2.26; IC025: 1.18). Injury, poisoning and procedural complications (ROR: 1.45 [1.42–1.47]; IC025: 0.45), Musculoskeletal and connective tissue disorders (ROR: 1.51 [1.46–1.53]; IC025: 0.51), and Neoplasms benign, malignant and unspecified (ROR: 1.27 [1.23–1.31]; IC025: 0.29) exceeded the positivity threshold in the ROR and BCPNN methods only, as shown in Table II.

Table II. Signal strength of golimumab ADEs across System organ classes (SOC) in the FAERS database

SOC	Case reports	ROR (95 % CI)	PRR (χ2)	EBGM (EBGM05)	IC (IC025)
Infections and infestations	23,600	4.25 (4.19–4.31)	3.63 (47,114)	3.61 (3.56)	1.85 (1.83)
Injury, poisoning and procedural complications	17,062	1.45 (1.42–1.47)	1.39 (2,033)	1.39 (1.36)	0.47 (0.45)
General disorders and administration site conditions	16,113	0.71 (0.7–0.72)	0.75 (1,669)	0.75 (0.74)	–0.42 (–0.44)
Musculoskeletal and connective tissue disorders	9,325	1.51 (1.46–1.53)	1.46 (1,412)	1.46 (1.43)	0.54 (0.51)
Gastrointestinal disorders	6,358	0.59 (0.58–0.61)	0.61 (1,697)	0.61 (0.60)	–0.71 (–0.74)
Nervous system disorders	4,635	0.44 (0.43–0.45)	0.46 (3,207)	0.46 (0.45)	–1.12 (–1.16)
Skin and subcutaneous tissue disorders	4,124	0.60 (0.58–0.62)	0.61 (1,063)	0.61 (0.59)	–0.71 (–0.75)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4,105	1.27 (1.23–1.31)	1.26 (226.5)	1.26 (1.22)	0.33 (0.29)
Surgical and medical procedures	4,003	2.39 (2.31–2.46)	2.34 (3,107)	2.34 (2.26)	1.22 (1.18)
Respiratory, thoracic and mediastinal disorders	3,598	0.61 (0.59–0.63)	0.62 (858.3)	0.62 (0.60)	–0.68 (–0.73)
Investigations	3,154	0.43 (0.41–0.44)	0.44 (2,350)	0.44 (0.43)	–1.17 (–1.23)
Vascular disorders	1,693	0.66 (0.63–0.69)	0.67 (289.8)	0.67 (0.63)	–0.59 (–0.66)
Psychiatric disorders	1,543	0.22 (0.21–0.23)	0.23 (4,219)	0.23 (0.22)	–2.12 (–2.19)
Cardiac disorders	1432	0.48 (0.45–0.50)	0.48 (806.1)	0.48 (0.46)	–1.05 (–1.12)
Eye disorders	1,415	0.56 (0.54–0.59)	0.57 (471.2)	0.57 (0.54)	–0.81 (–0.89)
Renal and urinary disorders	1,117	0.50 (0.47–0.53)	0.50 (567.1)	0.51 (0.47)	–1.00 (–1.08)
Immune system disorders	1,005	0.73 (0.68–0.77)	0.73 (103.6)	0.73 (0.68)	–0.46 (–0.55)
Metabolism and nutrition disorders	937	0.36 (0.34–0.38)	0.36 (1,073)	0.36 (0.34)	–1.46 (–1.56)
Blood and lymphatic system disorders	724	0.35 (0.33–0.38)	0.36 (860.8)	0.36 (0.33)	–1.49 (–1.60)
Hepatobiliary disorders	705	0.65 (0.60–0.70)	0.65 (133.5)	0.65 (0.60)	–0.62 (–0.73)
Reproductive system and breast disorders	456	0.46 (0.42–0.5)	0.46 (289.8)	0.46 (0.42)	–1.12 (–1.25)
Ear and labyrinth disorders	374	0.71 (0.65–0.79)	0.71 (42.7)	0.72 (0.65)	–0.48 (–0.63)

Pregnancy, puerperium and perinatal conditions	176	0.36 (0.31–0.41)	0.36 (205.6)	0.36 (0.31)	–1.49 (–1.70)
Endocrine disorders	164	0.52 (0.45–0.61)	0.52 (72.4)	0.52 (0.45)	–0.94 (–1.16)
Congenital, familial and genetic disorders	90	0.26 (0.21–0.32)	0.26 (188.9)	0.26 (0.21)	–1.94 (–2.23)

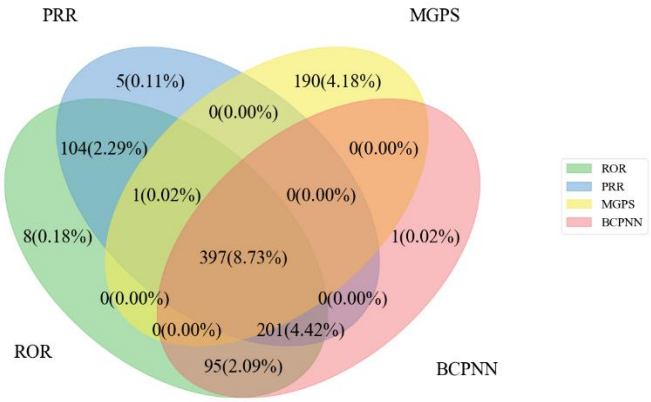
ADEs – adverse drug events, SOC – System organ class, ROR – reporting odds ratio, 95 % CI – 95% confidence interval, PRR - proportional reporting ratio, $\chi 2$ - chi-quared, EBGM – empirical Bayesian geometric mean, EBGM05 – the lower limit of the 95% CI of EBGM, IC – information component, IC025 – the lower limit of the 95 % CI of the IC.

The predominance of Infections and infestations is consistent with the known safety profile of TNF-α inhibition regarding infectious risks and supports further evaluation of infection-related events at the preferred term (PT) level. In contrast, the concordant signal for Surgical and medical procedures should be interpreted with caution, as this SOC contains procedure-related terms that may partially reflect underlying disease burden or clinical management rather than a direct pharmacological adverse effect (14).

Signal detection at the preferred term level

A total of 397 PT-level ADE signals simultaneously met the positivity criteria of all four algorithms, distributed across 25 SOCs (Fig. 2). Fig. 3 presents the top 50 adverse drug events associated with golimumab at the preferred term (PT) level, ranked by frequency of reports. The adverse events already documented in the prescribing information include pneumonia (*n* = 3,047), lower respiratory tract infection (*n* = 1,743), influenza (*n* = 1,121), infection (*n* = 1,030), nasopharyngitis (*n* = 847), sinusitis (*n* = 668), cellulitis (*n* = 632), bronchitis (*n* = 553), and herpes zoster (*n* = 483). The most frequently reported positive infection signals not listed on the label were urinary tract infection (*n* = 1,334), kidney infection (*n* = 299), ear infection (*n* = 252), and tooth abscess (*n* = 187). Serious infections associated with golimumab are subject to a black box warning in the prescribing information. A phase III randomized, placebo-controlled trial in patients with active psoriatic arthritis reported serious infections, including periodontitis, urinary tract infection, and ear infection, during intravenous golimumab treatment through week 60 (15). According to the literature, TNF-α is indispensable for the activation, differentiation, and recruitment of multiple immune cell populations, plays a pivotal role in maintaining granuloma integrity, and host defense against mycobacteria and intracellular pathogens. Consequently, TNF-α blockade substantially elevates the risk of bacterial, viral, and fungal infections (16, 17). In summary, these findings further underscore the importance of systematic infection risk management during golimumab therapy, encompassing comprehensive pre-treatment evaluation of active and latent

infections, patient education, and vigilant clinical and laboratory surveillance during and after



treatment (18).

Fig. 2. Venn plot of the number of positive adverse drug event reports for different methods.

Fig. 3. The top 50 ADEs of golimumab ranked by case reports at the PTs level. SOC – system organ class, PTs – preferred terms, ROR – Reporting Odds Ratio, 95 % CI – 95 % confidence interval, PRR – proportional reporting ratio, EBGM05 – the lower limit of the 95 % CI for EBGM, IC025 – the lower limit of the 95 % CI for IC, ADEs – adverse drug event).

Malignant events associated with golimumab are also subject to a black-box warning in the prescribing information. In this study, four malignancy events documented in the label with relatively high reporting frequencies were identified, namely neoplasm malignant (n = 416), skin cancer (n = 190), lymphoma (n = 155), and malignant melanoma (n = 148). Several clinical studies and meta-analyses have suggested that TNF-α inhibitors may increase the risk of certain types of tumors (19–22). Specifically, golimumab has been associated with an elevated risk of

skin cancer, particularly non-melanoma skin cancer. Furthermore, TNF-α inhibitors may also increase the risk of lymphoma, with higher risks observed in patients with long-standing chronic inflammation or those receiving high-dose therapy (21–22). The potential mechanism underlying malignancy events may be attributable to the physiological role of TNF-α in suppressing tumor growth within the normal immune system; TNF-α inhibitors block the binding of TNF-α to its receptor, thereby inhibiting its biological activity. Therefore, caution should be exercised when using this agent.

Fig. 4 shows the 30 highest-ranked positive signals by strength, of which 11 are listed in the prescribing information and 19 are not. The three signals with the highest ROR were administration site infection (*n* = 23; ROR: 143.87 [89.75–230.64]; PRR: 143.85 [χ^2: 2,447]; EBGM05: 67.45; IC025: 3.64), flavivirus infection (*n* = 24; ROR: 100.57 [64.49–156.83]; PRR: 100.55 [χ^2: 1,918]; EBGM05: 52.42; IC025: 3.64), and Zika virus infection (*n* = 13; ROR: 89.06 [49.02–161.80]; PRR: 89.05 [χ^2: 938]; EBGM05: 40.72; IC025: 2.73), all of which are absent from the prescribing information. Lower respiratory tract infection (*n* =1,743; ROR: 20.62 [19.65–21.64]; PRR: 20.34 [χ^2: 30,640]; EBGM05: 18.55; IC025: 4.20) and Dengue fever (*n* = 171; ROR: 37.84 [32.36–44.24]; PRR: 37.78 [χ^2: 5,631]; EBGM05: 29.78; IC025: 4.63) were noteworthy for combining both high report frequency and strong signal strength. It is noteworthy that the genera Flavivirus, as well as Zika virus and Dengue virus, all belong to the family Flaviviridae (23). Given that TNF-α plays a critical role in controlling viral infections by recruiting and activating macrophages, natural killer (NK) cells, T cells, and antigen-presenting cells, blockade of TNF-α may increase the risk of infection with viruses of the family Flaviviridae (24, 25). Currently, literature reports on viral infections induced by TNF-α inhibitors primarily involve herpesviruses, cytomegalovirus, and Epstein-Barr virus, with no reported cases of Flaviviridae family infections to date (15–18). Therefore, the adverse events related to the Flaviviridae family identified in this study represent a previously unreported and noteworthy pharmacovigilance finding. These signals warrant prospective clinical investigations to determine whether a causal relationship exists.

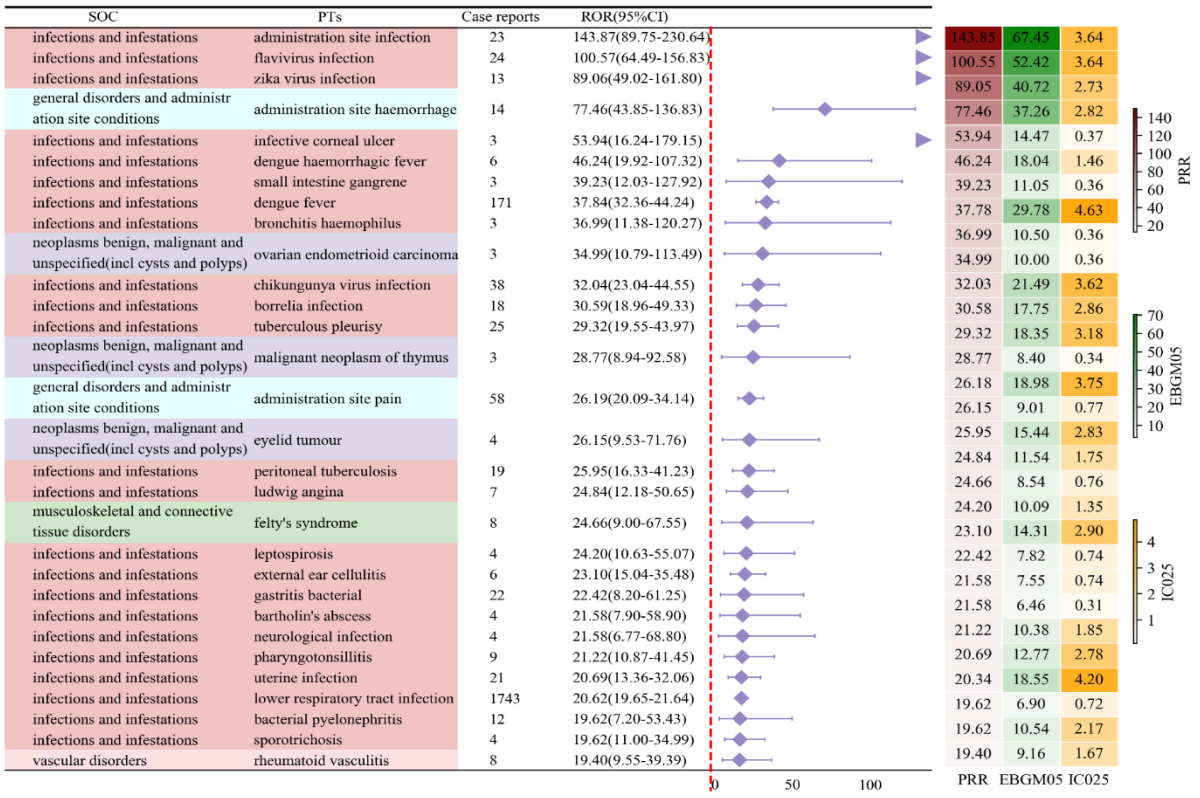


Fig. 4. The top 30 ADEs of golimumab ranked by ROR at the PTs level. SOC – system organ class, PTs – preferred terms, ROR – Reporting Odds Ratio, 95 % CI – 95 % confidence interval, PRR – proportional reporting ratio, EBGM05 – the lower limit of the 95 % CI for EBGM, IC025 – the lower limit of the 95 % CI for IC, ADEs – adverse drug event).

Fig. 5 presents 29 unlabeled malignancy signals, comprising 562 total reports. The six most frequently reported were basal cell carcinoma (*n* = 168), colon cancer (*n* = 81), cervix carcinoma (*n* = 33), invasive ductal breast carcinoma (*n* = 31), lung adenocarcinoma (*n* = 28), and rectal cancer (*n* = 26). By signal strength (ROR), the top three were ovarian endometrioid carcinoma (ROR: 34.99 [10.79–113.49]), malignant neoplasm of thymus (ROR: 28.77 [8.94–92.58]), and gingival cancer (ROR: 14.71 [4.65–46.50]). These findings are broadly corroborated by existing clinical evidence. Multiple clinical trials have reported malignancies in patients treated with golimumab, including breast cancer, basal cell carcinoma, lung adenocarcinoma, uterine cancer, Hodgkin's disease, and non-small cell lung cancer (16, 22, 26). In a study of golimumab for active RA, 8 patients (1.3 %) developed neoplasms, among whom 2 patients receiving 4 mg kg^{-1} developed colorectal cancer and gastric cancer, resp. (27). Collectively, these data suggest that golimumab may be associated with a broad spectrum of malignancies, and routine oncological surveillance is therefore advisable in clinical practice.

For patients with a history of malignancy, a comprehensive individualized assessment that weighs the tumor type, disease stage, metastatic risk, and patient preferences against the anticipated therapeutic benefits should be performed prior to initiating golimumab therapy.

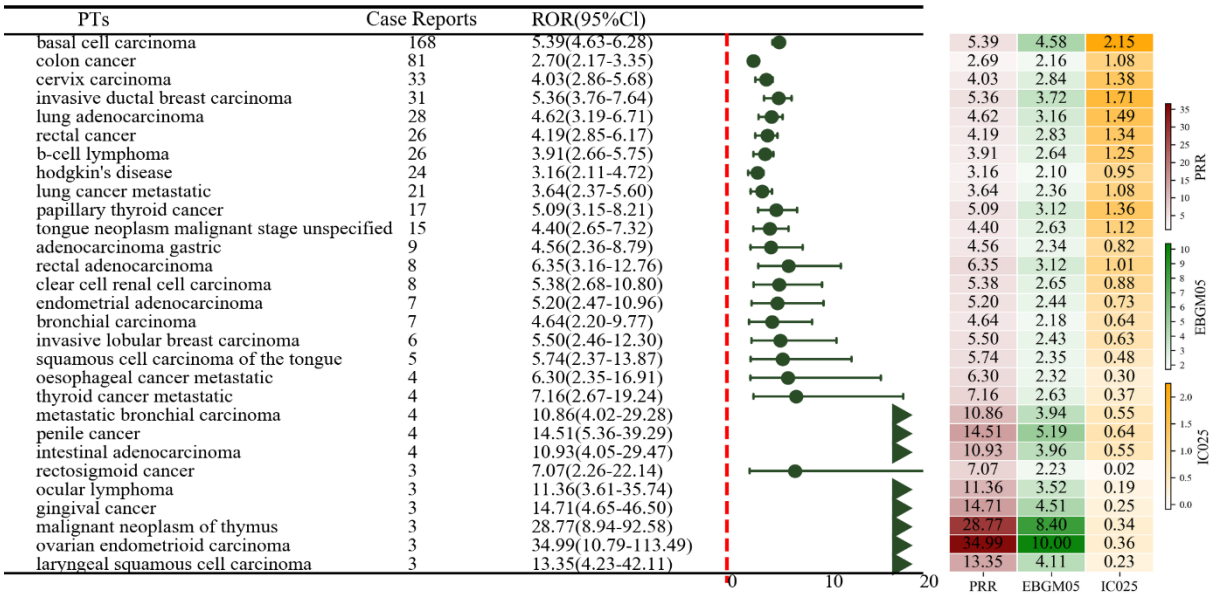


Fig. 5. Positive malignancy events not documented in the prescribing information. PTs – preferred terms, ROR – reporting odds ratio, 95 % CI – 95 % confidence interval, PRR – proportional reporting ratio, EBGM05 – the lower limit of the 95 % CI for EBGM, IC025 – the lower limit of the 95 % CI for IC).

Time-to-onset analysis and Weibull distribution testing

TTO analysis was performed on valid adverse event reports, with results presented in Fig. 6a. ADEs occurred most frequently within the first month of treatment (n =1,353, 14.5 %), although the frequency of reports declined progressively within the first 180 days following treatment initiation, 4,262 reports (45.7 %) still occurred beyond one-year post-initiation, suggesting that ADEs may exhibit a delayed onset. As shown in Table III, Weibull distribution fitting revealed a median onset time of 292 days (IQR: 71–835.8 days). The upper bound of the 95 % confidence interval for the shape parameter (β) was less than 1.0 (β = 0.72), consistent with an early-failure pattern (β < 1), indicating that the risk of ADEs is highest early in the treatment course and diminishes over time. The Kaplan-Meier curve in Fig. 6b shows the cumulative incidence of ADEs related to golimumab. The curve demonstrates that the cumulative incidence of adverse events increased rapidly within the first 400 days after treatment initiation (reaching 92 % by day 400), after which it gradually plateaued. Collectively,

although the risk is predominantly concentrated in the early phase, the occurrence of delayed-onset events nevertheless underscores the need for continued long-term follow-up in clinical practice (28).

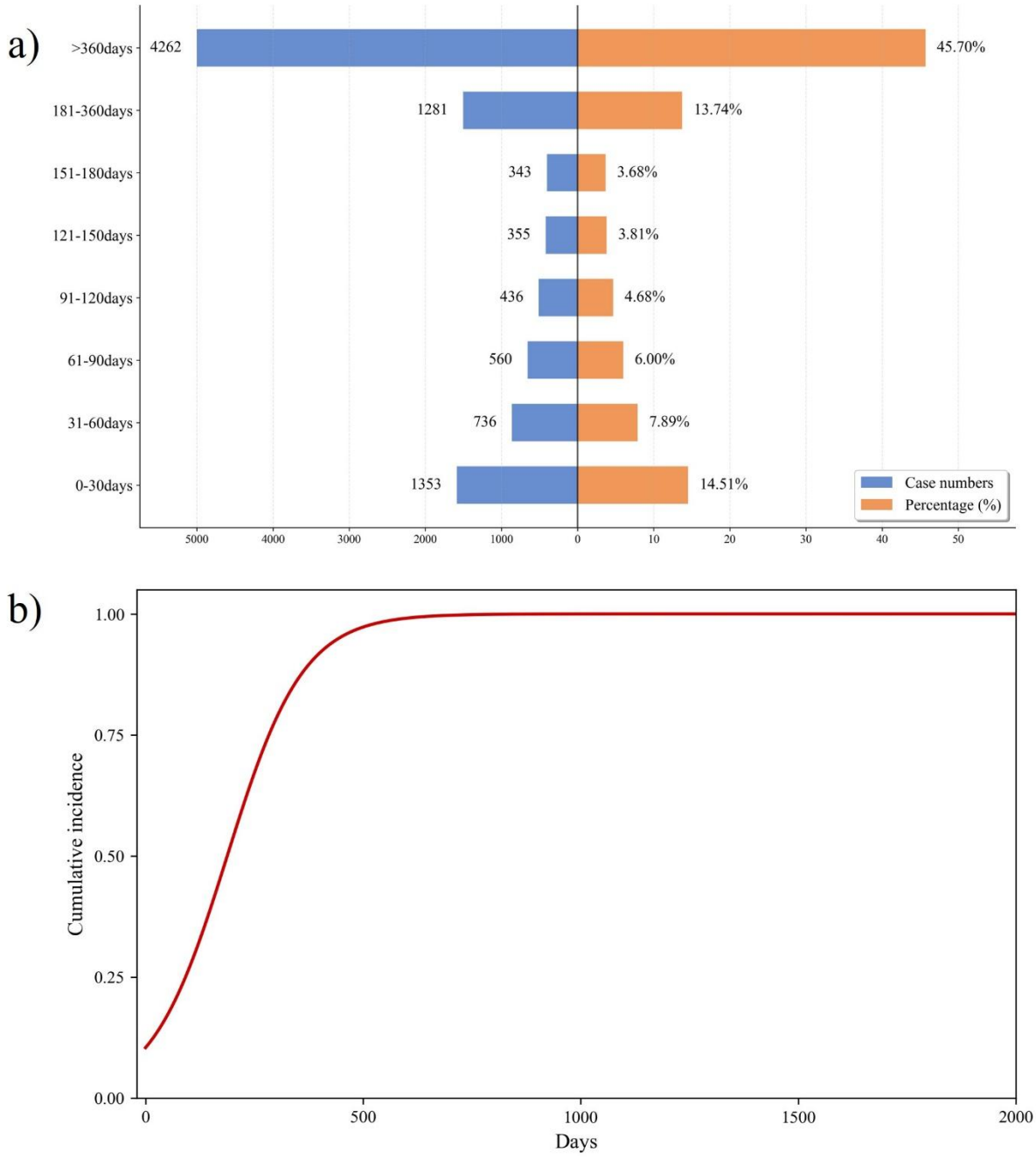


Fig. 6. Time to onset (TTO) analysis (counted in days) of golimumab-related ADEs: a) distribution of time to onset of golimumab-related ADEs; b) cumulative incidence of golimumab-related ADEs over time.

Table III. Time to onset (TTO) of golimumab associated adverse drug events and Weibull distribution analysis

TTO (days)	Weibull distribution

Case reports (*n*)	Median (d) (IQR)	Min-max	Scale parameter: α (95 % CI)	Shape parameter: β (95 % CI)	Type
9,326	292.0 (71.0–835.8)	1.0-5684.0	542.58(533.88-551.28)	0.72 (0.71-0.73)	Early failure

TTO– Time to onset, IQR – interquartile range, α – scale parameter of Weibull distribution, β – shape parameter of Weibull distribution (β < 1: early-failure pattern; β = 1: constant risk; β > 1: wear-out pattern), CI – confidence interval

*Limitations of the stud*y

The results of this study, which are based on analyses of the FAERS database, still have certain limitations. First, as a spontaneous pharmacovigilance reporting system, the FAERS database is inherently subject to underreporting, reporting bias, and varying data quality and completeness, all of which may affect the accuracy and reliability of signal detection. Second, disproportionality analyses using ROR, PRR, BCPNN and MGPS can only indicate statistical associations between drug exposure and adverse events; the signal strength merely quantifies the strength of association rather than absolute risk, and thus cannot be used to infer causality. Confirmation of causal relationships requires prospective clinical investigation and pharmaco-epidemiological studies. Third, FAERS data are predominantly contributed by reporters from North America and Europe, with a relatively low proportion of reports from Asian populations; this geographic imbalance may limit the generalizability of the findings. Fourth, the FAERS database has inherent limitations in controlling for important confounding factors, including concomitant medication use, disease severity, comorbidities, and a history of malignancy. This may introduce confounding bias into the signal associations identified in this study. To confirm these pharmacovigilance signals, future prospective cohort studies and pharmaco-epidemiological analyses with appropriate covariate adjustment are warranted (29).

CONCLUSIONS

This study provides a comprehensive real-world pharmacovigilance characterization of golimumab using four simultaneous disproportionality algorithms applied to a 16-year FAERS dataset. The concordant signal approach identified 397 positive ADE signals, including 29 previously unlabeled malignancy signals and novel Flaviviridae-related infection signals, collectively extending the known safety profile of golimumab beyond what is currently described in its prescribing information. Time-to-onset modelling further established a temporal pattern consistent with early failure, offering quantitative benchmarks for post-initiation

monitoring. These findings provide a real-world evidence basis to support regulatory review of the existing black-box warning and for evidence - based updates to prescribing guidance. Future prospective pharmaco-epidemiological studies with appropriate covariate adjustment will be essential to establish causal relationships and to further refine the long-term safety profile of golimumab across diverse patient populations.

Acronyms, abbreviations, symbols. – ADEs – adverse drug events, AS – ankylosing spondylitis, BCPNN – Bayesian confidence propagation neural network, C – Concomitant, CI – confidence interval, DEMO – patient demographic and administrative information, DRUG – drug-specific details, EBGM – empirical Bayesian geometric mean, EBGM05 – the lower limit of the 95% CI of EBGM, EMA – European Medicines Agency, FAERS – FDA Adverse Event Reporting System, FDA – Food and Drug Administration, I – interacting, IC – information component, IC025 – the lower limit of the 95% CI of the IC, INDI – indications for drug use, IQR – interquartile range, MedDRA – medical dictionary for regulatory activities, MGPS – multi-item gamma Poisson shrinker, MySQL – MySQL database management system, NK – natural killer, OUTC – patient outcomes dataset in FAERS, PRR – proportional reporting ratio, PS – primary suspect, PT – preferred term, RA – rheumatoid arthritis, REAC – adverse reaction records, ROR – reporting odds ratio, RPSR – report source, SAEs – serious adverse events, SD – standard deviation, SOC – system organ class, SS – secondary suspect, THER – therapy initiation and cessation dates, TNF-α – tumor necrosis factor-alpha, TTO – time to onset, α – scale parameter of Weibull distribution, β – shape parameter of Weibull distribution, χ^2– chi-squared test statistic.

Data availability. – The data supporting the findings of this study are publicly available from the FDA Adverse Event Reporting System (FAERS) database. FAERS data can be accessed at: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The aggregated dataset generated during the current study is available from the corresponding author upon reasonable request.

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