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Postmarketing safety evaluation of pemetrexed using FAERS and JADER databases

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Pemetrexed, a multi-target antifolate chemotherapeutic widely used in non-small cell lung cancer (NSCLC) and malignant pleural mesothelioma (MPM), is associated with various adverse drug events (ADEs), some of which may be underrecognized in clinical trials. This study conducted a comprehensive pharmacovigilance analysis using two major spontaneous reporting systems—FAERS (2004Q1–2024Q3) and JADER (2007Q1–2024Q3)—to evaluate pemetrexed-related ADEs. Disproportionality analysis was performed using four algorithms: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-Item Gamma Poisson Shrinker (MGPS). Time-to-onset (TTO) patterns were assessed using Weibull distribution modeling. A total of 12,026 and 4,522 pemetrexed-related ADE reports were retrieved from FAERS and JADER, respectively. The most frequently reported ADEs included hematologic toxicities (anemia, neutropenia, thrombocytopenia), gastrointestinal disorders (nausea, vomiting, diarrhea), and renal impairment. Strong safety signals were consistently identified for these events. Notably, novel ADE signals such as hepatobiliary injury, endocrine dysfunction, and thromboembolic events were observed in both databases. Subgroup analyses revealed sex- and age-specific ADE patterns, with younger patients and males showing distinct toxicity profiles. Sensitivity analysis excluding combination therapies confirmed the robustness of primary signals. TTO analysis revealed that most ADEs occurred within the first two months after pemetrexed initiation, with a median TTO of 27 days and a predominance of early failure patterns (Weibull $\beta < 1$), highlighting the importance of close monitoring during early treatment. Rare but severe ADEs, including myocarditis, sepsis, cholestasis, and pseudocellulitis, were identified, several of which are not currently listed in official drug labeling. This study provides a comprehensive safety assessment of pemetrexed, confirming known toxicities and identifying new safety signals. Continuous pharmacovigilance is essential to optimize its clinical use and improve patient safety.

Keywords Pemetrexed, Pharmacovigilance, FAERS and JADER, Adverse drug events (ADEs), Signal detection

Pemetrexed is a multi-target antifolate chemotherapeutic agent that exerts its antitumor effects by inhibiting folate-dependent metabolic pathways essential for cell replication. Its mechanism of action includes inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT)[1]. Pemetrexed has demonstrated significant antitumor activity in various solid tumors, including non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), breast cancer, and lymphoma[2,3]. Clinical studies have established pemetrexed as a first-line standard therapy for NSCLC and MPM[4,5]. Pemetrexed is administered intravenously, typically in 21-day cycles, with vitamin B_{12} and folic acid supplementation required to mitigate drug-associated toxicity[6].

In clinical trials, common pemetrexed-related adverse drug reactions (ADRs) include hematologic toxicity, gastrointestinal effects, and dermatologic reactions[7,8]. Notably, most ADRs can be effectively managed through supportive care and dose adjustments. However, given the stringent inclusion criteria, limited sample sizes, and short follow-up periods of clinical trials, certain ADRs may remain unrecognized or underreported.

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The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and the Japanese Adverse Drug Event Report (JADER) serve as post-marketing surveillance tools that facilitate early detection of drug safety concerns[9,10]. These databases aggregate adverse drug event (ADE) reports from healthcare professionals, patients, and pharmaceutical companies, providing rich real-world data for pharmacovigilance research[11]. Given the lack of large-scale and long-term safety data for pemetrexed, we conducted a post-marketing surveillance study to evaluate pemetrexed-associated ADEs reported in FAERS (Q1 2004 to Q3 2024) and JADER (Q1 2007 to Q3 2024). We comprehensively analyzed pemetrexed's system-specific adverse effects and their time-to-onset (TTO) while exploring sex- and age-based differences. The findings of this study will provide data-driven insights for clinicians and policymakers to optimize the safe use of pemetrexed in clinical practice.

Materials and methods

Data sources and collection

We conducted a retrospective pharmacovigilance study utilizing FAERS and JADER to investigate pemetrexed-associated ADEs. FAERS, one of the world's largest spontaneous reporting systems, compiles over 9 million reports from healthcare professionals and consumers, serving as a critical source for post-marketing drug safety surveillance[12]. FAERS comprises seven datasets: demographics (DEMO), drug information (DRUG), adverse reactions (REAC), patient outcomes (OUTC), report sources (RPSR), therapy start and end dates (THER), and indications (INDI). These datasets are linked using a unique CASEID identifier[13]. FAERS data are publicly available via the FDA website (http://www.fda.gov/).

JADER, managed by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, collects ADE reports from 2004 onward and includes reports from pharmaceutical companies and medical institutions. The database consists of four datasets: demographics (DEMO), drug information (DRUG), adverse reactions (REAC), and patient history (HIST)[14]. JADER data are accessible via the PMDA official website (https://www.pmda.go.jp/index.html).

To enhance reliability and reduce reporting bias, we integrated FAERS and JADER data for a comprehensive safety assessment. FAERS data from Q1 2004 to Q3 2024 and JADER data from Q1 2007 to Q3 2024 were analyzed. Drug name queries included generic name ("Pemetrexed"), chemical name ("MTA"), and brand name ("Alimta"), while in JADER, we searched the Japanese equivalent "ペメトレキセド". Duplicate reports were removed following FDA-recommended criteria, which prioritize the most recent report version based on the unique CASEID and the FDA_DT field (i.e., the date the FDA received the report), ensuring that only the latest and most complete record for each case is retained[12,15]. And data were standardized using MedDRA 27.0 terminology[16]. According to the MedDRA hierarchical framework, identified ADEs were categorized into preferred terms (PTs) and corresponding system organ classes (SOCs).

Signal detection and statistical analysis

To assess the association between pemetrexed and ADEs, we applied disproportionality analysis, including four widely used algorithms: Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Bayesian Confidence Propagation Neural Network (BCPNN), and Multi-Item Gamma Poisson Shrinker (MGPS). ROR and PRR are frequentist methods, with ROR being advantageous in correcting for reporting biases caused by low event counts[17]. PRR is less affected by the under-reporting of ADEs[18]. However, these methods are prone to false positives when the number of ADE reports is low[19]. BCPNN and MGPS, as Bayesian algorithms, provide a more stable assessment of disproportionate reporting by incorporating uncertainty in cases with low counts. BCPNN is particularly effective in integrating data from multiple sources and cross-validation, while MGPS is more suitable for detecting rare ADEs[20,21]. Bayesian methods reduce false-positive signals but are computationally more complex[22]. To improve signal detection accuracy, we applied all four algorithms and considered an ADE as a positive signal if it met the predefined thresholds for all methods[23] (**Supplementary Table S1**). Bonferroni correction was used to adjust for multiple comparisons and control type I error risk. All statistical analyses were conducted using R software version 4.3.3.

Time-to-Onset analysis

The time-to-onset (TTO) of pemetrexed-related ADEs was defined as the interval between the drug administration start date (START_DT) and the ADE occurrence date (EVENT_DT). Records with ADEs occurring before drug administration were excluded from the analysis. We applied Weibull distribution modeling to analyze TTO characteristics, using the 95% confidence interval (CI) of the shape parameter (β) to determine ADE risk patterns over time[24]. Specifically, $\beta < 1$ indicates a decreasing risk over time (early failure pattern), $\beta \approx 1$ suggests a constant risk (random failure pattern), $\beta > 1$ signifies an increasing risk over time (wear-out failure pattern)[23]. Kruskal-Wallis tests were used to compare TTO distributions across ADE groups, and Kaplan-Meier curves were generated to visualize the cumulative incidence of ADEs over time[25].

Results

Descriptive characteristics

A total of 12,026 pemetrexed-related ADE reports were retrieved from FAERS (Q1 2004–Q3 2024) and 4,522 reports from JADER (Q1 2007–Q3 2024) (Fig. 1). The number of ADE reports in FAERS increased steadily, exceeding 400 reports per year from 2018 onwards (Fig. 2A). In JADER, over 100 reports per year were recorded consistently (Fig. 2B).

The demographic characteristics of ADE reports, including age, sex, weight, indications, and outcomes, are summarized in Tables 1 and 2. In FAERS, male patients accounted for 56.5% ($n = 6,791$) of reports, whereas

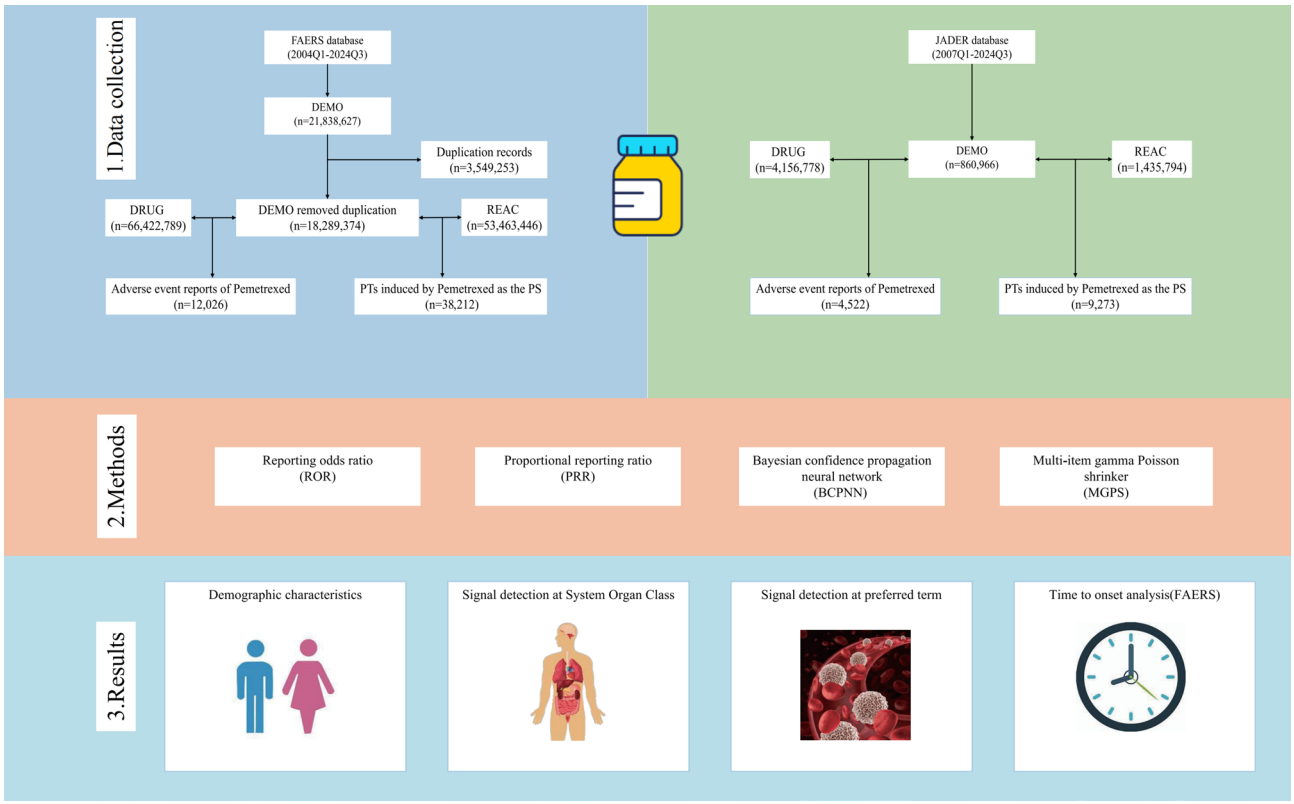

Fig. 1. Flowchart of the study outlining data collection and preprocessing, signal strength calculation through disproportionality analysis, and results presentation. FAERS: FDA Adverse Event Reporting System, JADER: Japanese Adverse Drug Event Report, Q1: first quarter, Q4: fourth quarter, PT: preferred term, PS: primary suspect.

female patients comprised 35.9% (n = 4,322). Among reports with known age, patients aged 65 years or older constituted the largest group (n = 4,378, 36.4%). Weight information was missing in 65.1% of cases (n = 7,830), but for those with available data, most patients weighed 50–100 kg (30.1%). The majority of reports originated from healthcare professionals (n = 7,246, 60.2%), with serious outcomes including hospitalization (n = 3,902, 32.4%) and death (n = 2,597, 21.6%). Pemetrexed was primarily indicated for NSCLC (n = 3,046, 25.3%), followed by lung adenocarcinoma (n = 1,402, 11.7%) (Table 1). Similarly, in JADER, male patients accounted for 69.3% (n = 3,136) of reports, a significantly higher proportion than females (22.9%, n = 1,034). Patients aged < 65 years (n = 2,446, 54.1%) outnumbered those ≥ 65 years (n = 1,875, 41.5%). Among individuals with available weight data, most were in the 50–100 kg range (n = 1,653, 36.6%). Recovery rates were 57%, but 7.7% of reports involved fatalities. Consistent with FAERS, NSCLC (n = 3,046, 25.3%) was the most common indication (Table 2).

Signal detection at the SOC level

Pemetrexed-related ADEs were mapped to their respective SOCs, and the number of reports for each SOC was ranked. The positive thresholds for the four signal detection methods (ROR, PRR, BCPNN, and MGPS) used in this study are summarized in **Supplementary Table S1**. FAERS data contained 27 SOCs, while JADER included 23 SOCs. The top three SOCs differed between the databases: FAERS: General disorders and administration site conditions (n = 5,074), Blood and lymphatic system disorders (n = 4,003), Gastrointestinal disorders (n = 3,804) (Fig. 2C). JADER: Investigations (n = 1,719), Respiratory, thoracic and mediastinal disorders (n = 1,310), Blood and lymphatic system disorders (n = 1,127) (Fig. 2D). Despite these differences, four SOCs overlapped in both databases: Investigations, Respiratory, thoracic and mediastinal disorders, Blood and lymphatic system disorders, and Gastrointestinal disorders. Disproportionality analysis identified 12 SOCs in FAERS and 7 SOCs in JADER that met the ROR-positive threshold (Fig. 2E and F). The strongest SOC-level signals in FAERS were: Blood and lymphatic system disorders (ROR: 6.72 [6.5–6.94]), Neoplasms benign, malignant, and unspecified (ROR: 2.17 [2.08–2.27]), Renal and urinary disorders (ROR: 2.42 [2.3–2.54]), Hepatobiliary disorders (ROR: 2.37 [2.21–2.54]), Endocrine disorders (ROR: 2.81 [2.49–3.16]) (Table 3). In JADER, only Endocrine disorders (ROR: 2.52 [2.27–2.79]) met the positive threshold across all four signal detection methods (Table 4).

Signal detection at the PT level

Subsequently, considering only the frequency of reported cases, we identified the top 20 PTs in both cohorts. In FAERS, the most frequently reported PT was Anemia (n = 701, 1.83%), followed by Pancytopenia (n = 649, 1.70%), Nausea (n = 644, 1.69%), Thrombocytopenia (n = 556, 1.46%), and Neutropenia (n = 555, 1.45%)

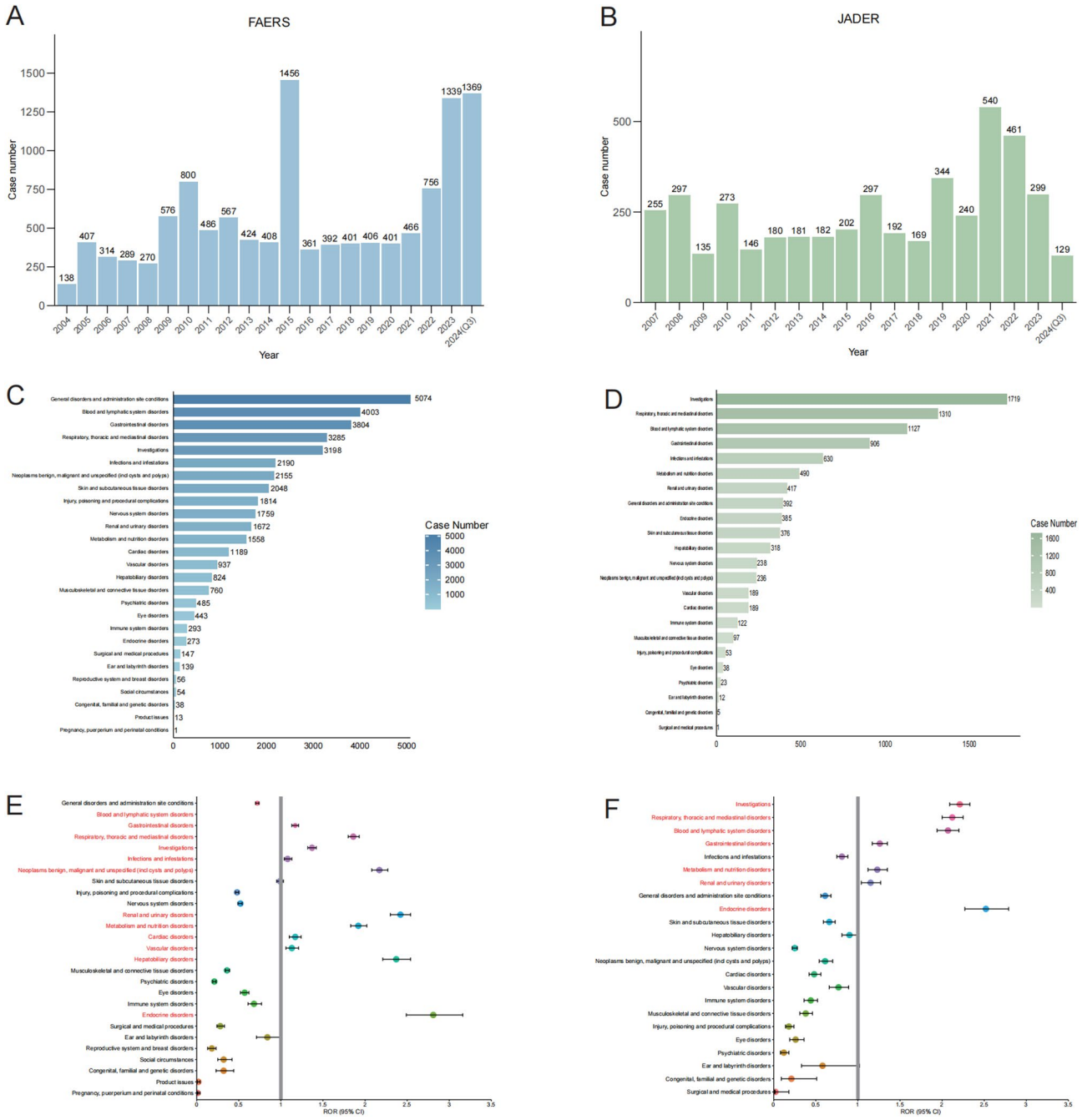

Fig. 2. Signal detection at the SOC level. Annual ADE reports in the FAERS (**A**) and JADER (**B**) databases are presented as bar charts. The number of pemetrexed -induced ADEs at the SOC level in FAERS (**C**) and JADER (**D**) is displayed. Signal detection results at the SOC level in FAERS (**E**) and JADER (**F**) are shown, with ROR values and their 95% confidence intervals (95% CI) visualized. SOC: System Organ Class, ADE: adverse drug event, FAERS: FDA Adverse Event Reporting System, JADER: Japanese Adverse Drug Event Report, ROR: reporting odds ratio.

(Fig. 3A). In contrast, the top five PTs in the JADER database were Interstitial lung disease ($n = 677$, 7.3%), Neutrophil count decreased ($n = 540$, 5.82%), White blood cell count decreased ($n = 347$, 3.74%), Platelet count decreased ($n = 323$, 3.48%), and Anemia ($n = 307$, 3.31%) (Fig. 3B). Additionally, we identified 12 overlapping signals: Anemia, Nausea, Thrombocytopenia, Neutropenia, Diarrhea, Vomiting, Pyrexia, Pneumonia, Febrile neutropenia, Rash, Decreased appetite, and Interstitial lung disease.

Using disproportionality analysis, we calculated the signal strength of each PT and filtered out signals that met positive thresholds across all detection methods. In FAERS, 400 signals met the criteria, while 58 signals were identified in JADER. Signals were ranked in descending order based on report cases and grouped by SOC, with forest plots illustrating the ROR values and 95% confidence intervals (CIs) for the top 20 signals in each cohort.

Characteristics	Number of reports (%)
Sex	
Female	4322(35.90)
Male	6791(56.50)
Unknown	913(7.60)
Age	
< 18 years	18(0.10)
18–64 years	4137(34.40)
≥ 65 years	4378(36.40)
Unknown	3493(29.10)
Weight	
< 50 kg	376(3.10)
50–100 kg	3617(30.10)
> 100 kg	203(1.70)
Unknown	7830(65.10)
Reported Countries (top five)	
United States	3776(31.40)
France	2006(16.70)
Italy	913(7.60)
Japan	884(7.40)
Germany	809(6.70)
Reported person	
Health professional	7246(60.20)
Consumer	4589(38.20)
Unknown	191(1.60)
Outcome	
Hospitalization-initial or prolonged	3902(32.40)
Life-threatening	660(5.50)
Disability	110(0.90)
Required intervention	6(0.00)
Death	2597(21.60)
Other serious outcomes	3476(28.90)
Unknown	1275(10.60)
Indication (top five)	
Non-small cell lung cancer	3046(25.30)
Lung adenocarcinoma	1402(11.70)
Lung neoplasm malignant	1276(10.60)
Lung adenocarcinoma stage iv	595(4.90)
Non-small cell lung cancer metastatic	505(4.20)

Table 1. Demographic characteristics of ADEs reported in the FAERS database with pemetrexed as the primary suspect drug.

Generally, higher ROR values indicated stronger associations with pemetrexed. In FAERS, several PTs had a high number of reports and strong signal intensity, including Pancytopenia ($n = 649$, ROR: 19.09 [17.66–20.64], PRR: 18.78, EBGM05: 17.37, IC025: 4.1), Mucosal inflammation ($n = 236$, ROR: 14.58 [12.82–16.58], PRR: 14.49, EBGM05: 12.89, IC025: 3.65), and Febrile neutropenia ($n = 415$, ROR: 10.18 [9.24–11.22], PRR: 10.08, EBGM05: 9.24, IC025: 3.18) (Fig. 4A). Although some PTs had a lower number of reports, they exhibited extremely high signal intensity, such as Pseudocellulitis ($n = 45$, ROR: 746.23 [519.47–1071.97], PRR: 745.35, EBGM05: 358.7, IC025: 8.43), Scleroderma-like reaction ($n = 13$, ROR: 154.64 [87.18–274.3], PRR: 154.59, EBGM05: 86.19, IC025: 6.31), and Hypercreatininaemia ($n = 20$, ROR: 66.45 [42.42–104.07], PRR: 66.41, EBGM05: 43.58, IC025: 5.34) (**Supplementary Table S2**). Notably, we identified several novel signals not listed in the drug label, including Sepsis, Respiratory failure, Electrolyte imbalance, Myocarditis, Gastrointestinal perforation, Hypothyroidism, and Cholestasis. **Supplementary Table S2** provides the full results of the FAERS analysis.

In the JADER database, the top 20 signals identified are listed in Fig. 4B. PTs with high report cases and strong signal intensity included Pneumonitis ($n = 167$, ROR: 7.47 [6.38–8.73], PRR: 7.35, EBGM05: 6.19, IC025: 1.15), Neutrophil count decreased ($n = 540$, ROR: 4.86 [4.45–5.3], PRR: 4.63, EBGM05: 4.2, IC025: 0.51), and Immune-mediated dermatitis ($n = 36$, ROR: 15.19 [10.78–21.4], PRR: 15.13, EBGM05: 10.41, IC025: 2.12). New signals included Cholangitis sclerosing ($n = 13$, ROR: 5.94 [3.41–10.34], PRR: 5.93, EBGM05: 3.62, IC025: 0.85), Cytokine release syndrome ($n = 35$, ROR: 3.35 [2.4–4.69], PRR: 3.34, EBGM05: 2.49, IC025: 0.05),

Characteristics	Number of reports (%)
Sex	
Female	1034(22.90)
Male	3136(69.30)
Unknown	352(7.80)
Age	
< 65 years	2446(54.10)
≥ 65 years	1875(41.50)
Unknown	201(4.40)
Weight	
< 50 kg	542(12.00)
50–100 kg	1653(36.60)
> 100 kg	2(0.00)
Unknown	2325(51.40)
Outcome	
Recovery (recovery but with sequelae)	109(1.20)
Rehabilitation	3234(34.90)
Minor rehabilitation	1935(20.90)
Death	712(7.70)
Non-rehabilitation	852(9.20)
Missing	2431(26.20)
Indication (top three)	
Non-small cell lung cancer	3046(25.30)
Lung adenocarcinoma	1402(11.70)
Lung neoplasm malignant	1276(10.60)

Table 2. Demographic characteristics of ADEs reported in the JADER database with pemetrexed as the primary suspect drug.

Adrenocorticotropic hormone deficiency ($n = 27$, ROR: 5.86 [3.99–8.62], PRR: 5.85, EBGM05: 4.11, IC025: 0.83), Hypophysitis ($n = 18$, ROR: 7.42 [4.62–11.91], PRR: 7.4, EBGM05: 4.78, IC025: 1.16), and Pleurisy ($n = 14$, ROR: 3.8 [2.23–6.45], PRR: 3.79, EBGM05: 2.39, IC025: 0.23). **Supplementary Table S3** provides the full results of the JADER analysis.

Combining results from both databases, we identified 35 positive signals appearing in both datasets. To visually present the most significant ADE signals, we generated volcano plots for FAERS and JADER (**Supplementary Figure S1**). These plots display 400 and 58 positive signals, respectively. Notable strong positive signals identified in FAERS included Pseudocellulitis and Erysipeloid, while in JADER, remarkable signals included Renal function test abnormal and Immune-mediated dermatitis. These findings highlight ADE signals highly associated with pemetrexed, emphasizing the importance of monitoring specific reactions in diverse populations based on pharmacovigilance database data.

Subgroup analysis

To minimize the influence of confounding factors, we conducted a subgroup analysis of pemetrexed-associated adverse events (AEs) using data from the FAERS and JADER databases. Based on the positive signal criteria (**Supplementary Figure S2**), we identified the 15 most common AEs in each subgroup. In the FAERS database, sex-specific AEs included interstitial lung disease and sepsis in males, while females exhibited tubulointerstitial nephritis, hypokalaemia, and pulmonary embolism (**Supplementary Figure S2A-B**). Among patients under 65 years old, the primary signals included acute kidney injury and tubulointerstitial nephritis, whereas patients aged 65 years or older more frequently experienced pyrexia, interstitial lung disease, and leukopenia (**Supplementary Figure S2C-D**).

In the JADER database, we also observed sex- and age-specific AEs. Male-specific events included interstitial lung disease and immune-mediated conditions such as immune-mediated adrenal insufficiency, immune-mediated dermatitis, and immune-mediated lung disease. Female-specific events included hypertension, decreased hemoglobin levels, and increased blood creatinine levels (**Supplementary Figure S2E-F**). For patients under 65 years old, the primary signals included decreased appetite and vomiting, while those aged 65 years or older exhibited a higher prevalence of tubulointerstitial nephritis and immune-mediated adrenal insufficiency (**Supplementary Figure S2G-H**).

Sensitivity analysis

In clinical practice, pemetrexed is often administered in combination with other chemotherapeutic agents such as cisplatin and carboplatin to enhance antitumor efficacy. To eliminate the potential influence of combination therapy on our findings, we conducted a sensitivity analysis. After excluding cases involving co-administration

System Organ Class	SOC code	Case number	ROR (95% CI)	PRR(χ2)	EBGM(EBGM05)	IC(IC025)
General disorders and administration site conditions	10,018,065	5074	0.72(0.7–0.74)	0.76(482.95)	0.76(0.74)	−0.4(−0.45)
Blood and lymphatic system disorders	10,005,329	4003	6.72(6.5–6.94)	6.12(17369.76)	6.1(5.93)	2.61(2.56)
Gastrointestinal disorders	10,017,947	3804	1.17(1.13–1.21)	1.16(86.65)	1.15(1.12)	0.21(0.16)
Respiratory, thoracic and mediastinal disorders	10,038,738	3285	1.86(1.8–1.93)	1.79(1194.41)	1.79(1.73)	0.84(0.78)
Investigations	10,022,891	3198	1.37(1.32–1.42)	1.34(292.52)	1.34(1.3)	0.42(0.37)
Infections and infestations	10,021,881	2190	1.08(1.04–1.13)	1.08(13.45)	1.08(1.04)	0.11(0.05)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10,029,104	2155	2.17(2.08–2.27)	2.11(1288.78)	2.11(2.03)	1.08(1.01)
Skin and subcutaneous tissue disorders	10,040,785	2048	0.99(0.95–1.03)	0.99(0.25)	0.99(0.95)	−0.02(−0.08)
Injury, poisoning and procedural complications	10,022,117	1814	0.48(0.46–0.5)	0.5(979.05)	0.5(0.48)	−0.99(−1.06)
Nervous system disorders	10,029,205	1759	0.52(0.49–0.54)	0.54(763.67)	0.54(0.52)	−0.89(−0.96)
Renal and urinary disorders	10,038,359	1672	2.42(2.3–2.54)	2.36(1329.08)	2.35(2.26)	1.24(1.16)
Metabolism and nutrition disorders	10,027,433	1558	1.92(1.83–2.02)	1.88(658.81)	1.88(1.8)	0.91(0.84)
Cardiac disorders	10,007,541	1189	1.17(1.1–1.24)	1.16(27.74)	1.16(1.11)	0.22(0.13)
Vascular disorders	10,047,065	937	1.13(1.06–1.21)	1.13(13.53)	1.13(1.07)	0.17(0.08)
Hepatobiliary disorders	10,019,805	824	2.37(2.21–2.54)	2.34(638.66)	2.34(2.21)	1.23(1.12)
Musculoskeletal and connective tissue disorders	10,028,395	760	0.36(0.34–0.39)	0.37(844.08)	0.37(0.35)	−1.42(−1.53)
Psychiatric disorders	10,037,175	485	0.21(0.19–0.23)	0.22(1417.58)	0.22(0.2)	−2.18(−2.31)
Eye disorders	10,015,919	443	0.57(0.52–0.62)	0.57(143.56)	0.57(0.53)	−0.8(−0.94)
Immune system disorders	10,021,428	293	0.68(0.61–0.77)	0.68(42.92)	0.69(0.62)	−0.55(−0.71)
Endocrine disorders	10,014,698	273	2.81(2.49–3.16)	2.79(314.53)	2.79(2.53)	1.48(1.31)
Surgical and medical procedures	10,042,613	147	0.28(0.24–0.33)	0.28(272.11)	0.28(0.25)	−1.82(−2.06)
Ear and labyrinth disorders	10,013,993	139	0.84(0.71–0.99)	0.84(4.48)	0.84(0.73)	−0.26(−0.5)
Reproductive system and breast disorders	10,038,604	56	0.18(0.13–0.23)	0.18(216.86)	0.18(0.14)	−2.5(−2.88)
Social circumstances	10,041,244	54	0.32(0.25–0.42)	0.32(76.9)	0.32(0.26)	−1.63(−2.02)
Congenital, familial and genetic disorders	10,010,331	38	0.32(0.23–0.44)	0.32(54.04)	0.32(0.25)	−1.63(−2.09)
Product issues	10,077,536	13	0.02(0.01–0.04)	0.02(588.02)	0.02(0.01)	−5.54(−6.31)
Pregnancy, puerperium and perinatal conditions	10,036,585	1	0.01(0–0.04)	0.01(164.7)	0.01(0)	−7.37(−9.41)

Table 3. Signal detection at the SOC level in FAERS.

with other drugs, we identified 1,124 reports. Persistent adverse reactions included pancytopenia, pneumonia, febrile neutropenia, neutropenia, thrombocytopenia, anemia, renal failure, pleural effusion, and erysipelas (**Supplementary Table S4**).

Time-to-Onset analysis

Due to the limited number of valid time-to-onset (TTO) reports in the JADER database, we performed statistical analysis only on TTO reports from the FAERS database. Pemetrexed-related ADEs primarily occurred within the first two months post-administration (n = 3,357, 68.12%). After the first two months, the number of TTO reports gradually declined over time (Fig. 5A).

A total of 4,928 (41.0%) valid TTO reports were identified in FAERS, with a median TTO of 27 days and an interquartile range (IQR) of 7 to 84 days (Fig. 5B). The Weibull distribution analysis for FAERS TTO data indicated that the upper limit of the 95% confidence interval (CI) for the shape parameter (β) was less than 1 (0.70), suggesting an early failure type, implying that the probability of ADE occurrence gradually decreases over time (Fig. 5B).

Furthermore, we analyzed TTO reports at the SOC level. Among the 24 SOCs with at least 10 valid TTO reports, significant differences in TTO distributions were observed (P < 0.0001, Fig. 5C). The SOCs with the shortest median TTO included "Skin and subcutaneous tissue disorders" (median TTO: 12 days), "Gastrointestinal disorders" (median TTO: 15 days), and "Reproductive system and breast disorders" (median TTO: 15.5 days). In contrast, the SOCs with the longest median TTO included "Ear and labyrinth disorders" (median TTO: 49.5 days), "Musculoskeletal and connective tissue disorders" (median TTO: 48 days), and "Neoplasms benign, malignant, and unspecified (including cysts and polyps)" (median TTO: 44 days) (**Supplementary Table S5**). The cumulative incidence of ADEs over time was depicted using Kaplan-Meier curves (Fig. 5D).

Discussion

Baseline characteristics

This study systematically analyzed the baseline characteristics of pemetrexed-associated ADEs in the FAERS and JADER databases, revealing significant differences in population characteristics between the two datasets. Both FAERS and JADER reported more ADEs in male patients, likely due to the higher NSCLC incidence in men, driven by smoking prevalence, genetic factors, and environmental exposures[26].In terms of regional distribution, FAERS primarily includes cases from the United States and multiple European countries, whereas JADER is almost exclusively based on Japanese data. Despite differences in regional coverage, the indications for pemetrexed

System Organ Class	SOC code	Case number	ROR (95%CI)	PRR(χ2)	EBGM(EBGM05)	IC(IC025)
Investigations	10,022,891	1719	2.21(2.09–2.33)	1.98(913.16)	1.97(1.89)	0.98(−0.69)
Respiratory, thoracic and mediastinal disorders	10,038,738	1310	2.12(2–2.25)	1.96(656.73)	1.95(1.86)	0.96(−0.7)
Blood and lymphatic system disorders	10,005,329	1127	2.07(1.94–2.2)	1.94(538.74)	1.93(1.83)	0.95(−0.72)
Gastrointestinal disorders	10,017,947	906	1.26(1.17–1.35)	1.23(42.23)	1.23(1.16)	0.3(−1.37)
Infections and infestations	10,021,881	630	0.81(0.75–0.88)	0.82(25.57)	0.83(0.77)	−0.28(−1.94)
Metabolism and nutrition disorders	10,027,433	490	1.23(1.12–1.35)	1.22(19.68)	1.22(1.13)	0.28(−1.38)
Renal and urinary disorders	10,038,359	417	1.15(1.04–1.27)	1.15(8)	1.14(1.05)	0.2(−1.47)
General disorders and administration site conditions	10,018,065	392	0.61(0.56–0.68)	0.63(90.2)	0.63(0.58)	−0.66(−2.33)
Endocrine disorders	10,014,698	385	2.52(2.27–2.79)	2.45(332.46)	2.43(2.23)	1.28(−0.38)
Skin and subcutaneous tissue disorders	10,040,785	376	0.66(0.59–0.73)	0.67(63.12)	0.67(0.62)	−0.57(−2.23)
Hepatobiliary disorders	10,019,805	318	0.9(0.81–1.01)	0.91(3.07)	0.91(0.83)	−0.14(−1.8)
Nervous system disorders	10,029,205	238	0.25(0.22–0.28)	0.27(521.72)	0.27(0.24)	−1.89(−3.55)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10,029,104	236	0.61(0.54–0.7)	0.62(55.62)	0.63(0.56)	−0.68(−2.34)
Cardiac disorders	10,007,541	189	0.48(0.42–0.56)	0.49(103.01)	0.49(0.44)	−1.02(−2.68)
Vascular disorders	10,047,065	189	0.77(0.66–0.89)	0.77(12.9)	0.77(0.69)	−0.37(−2.04)
Immune system disorders	10,021,428	122	0.44(0.36–0.52)	0.44(88.01)	0.44(0.38)	−1.17(−2.84)
Musculoskeletal and connective tissue disorders	10,028,395	97	0.38(0.31–0.46)	0.39(96.52)	0.39(0.33)	−1.36(−3.03)
Injury, poisoning and procedural complications	10,022,117	53	0.18(0.14–0.24)	0.19(193.04)	0.19(0.15)	−2.41(−4.08)
Eye disorders	10,015,919	38	0.26(0.19–0.36)	0.27(77.38)	0.27(0.21)	−1.9(−3.56)
Psychiatric disorders	10,037,175	23	0.12(0.08–0.18)	0.12(149.89)	0.12(0.09)	−3.04(−4.71)
Ear and labyrinth disorders	10,013,993	12	0.58(0.33–1.02)	0.58(3.66)	0.58(0.36)	−0.78(−2.45)
Congenital, familial and genetic disorders	10,010,331	5	0.21(0.09–0.51)	0.21(14.62)	0.21(0.1)	−2.23(−3.89)
Surgical and medical procedures	10,042,613	1	0.02(0–0.18)	0.02(38.47)	0.02(0)	−5.32(−6.99)

Table 4. Signal detection at the SOC level in JADER.

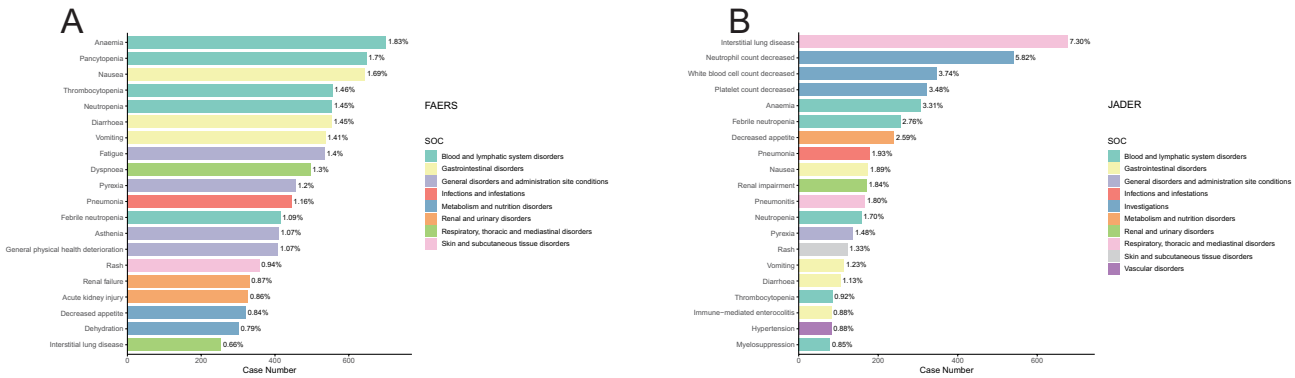

Fig. 3. Bar plot displaying the top 20 PT statistics in the FAERS (**A**) and JADER (**B**) databases. PT: preferred term, FAERS: FDA Adverse Event Reporting System, JADER: Japanese Adverse Drug Event Report.

remain highly consistent between the two databases, indicating stable clinical application patterns. However, the significant differences in patient baseline characteristics across databases must be carefully considered when interpreting ADE research and drug safety assessments. FAERS primarily captured ADEs among elderly male patients, while JADER had a higher proportion of younger male patients. These differences likely reflect regional variations in disease prevalence, treatment patterns, and reporting behaviors. The predominance of reports from healthcare professionals in FAERS and the regional exclusivity of JADER to Japan underscore the importance of contextualizing findings within their respective healthcare systems. These findings highlight the need to consider database structure and population characteristics when interpreting pharmacovigilance results.

SOCs meeting positive signal thresholds in both databases

Blood and lymphatic system disorders

Pemetrexed is an antifolate chemotherapeutic agent widely used for treating NSCLC, with hematologic toxicity primarily manifesting as myelosuppression, including leukopenia, anemia, and thrombocytopenia. Our real-world analysis of pemetrexed confirmed these adverse reactions. This adverse effect arises from pemetrexed's inhibition of folate-dependent metabolic pathways, blocking DNA and RNA synthesis, thereby affecting both

Fig. 4. Signal detection at the PT level. The forest plot displays ROR values with confidence intervals for the top 20 positive signals (ranked by case count) associated with pemetrexed at the PT level in FAERS (**A**) and JADER (**B**), categorized by SOC. Adjacent to this, the heatmap visualizes PRR, EBGM05, and IC025 values, providing a comprehensive assessment of signal strength across different metrics. ROR: Reporting Odds Ratio, PRR: Proportional Reporting Ratio, EBGM05: lower limit of the 95% CI of EBGM, IC025: lower limit of the 95% CI of the IC, SOC: System Organ Class, PT: preferred term, FAERS: FDA Adverse Event Reporting System, JADER: Japanese Adverse Drug Event Report.

cancer cell proliferation and bone marrow hematopoiesis[27]. Studies have shown that pemetrexed inhibits TS and DHFR, disrupting thymidine and purine synthesis, leading to cell cycle arrest and apoptosis[28]. Additionally, inhibition of folate metabolic enzymes, such as TS and DHFR, depletes intracellular folate derivatives (e.g., 5-methyltetrahydrofolate), impairing erythropoiesis and potentially resulting in anemia. While pemetrexed has relatively mild hematologic toxicity compared to other chemotherapy regimens, close monitoring of blood counts remains essential for optimizing treatment outcomes[29].

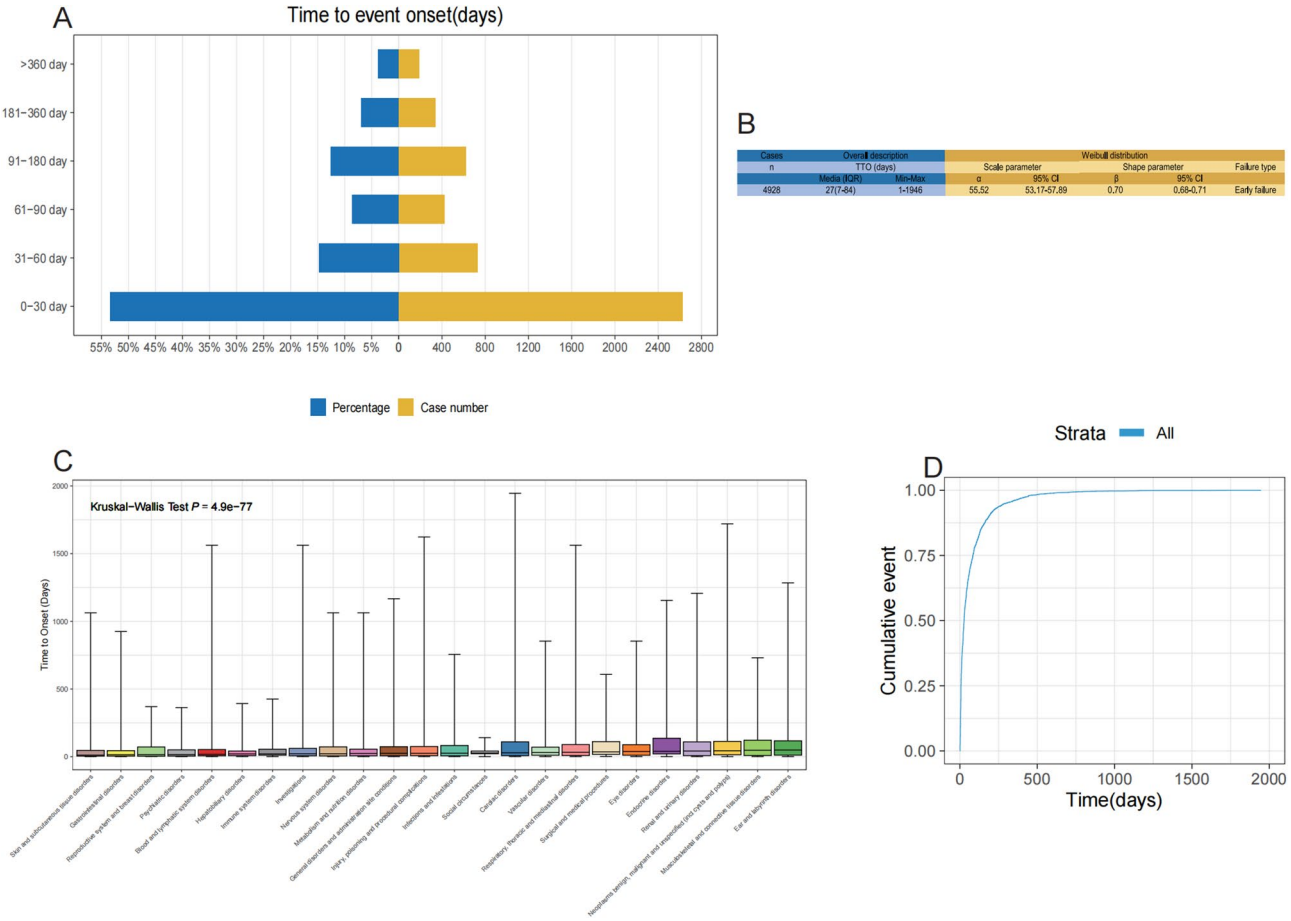

Fig. 5. Time-to-onset (TTO) analysis (in days) of pemetrexed-related ADEs. (**A**) Bar graphs display the number and proportion of ADE reports across different time intervals. (**B**) Overall description and Weibull distribution analysis of effective TTO reports, highlighting the median occurrence time along with minimum and maximum values. (**C**) Box plot of TTO at the SOC level, where the bold line within the box represents the median TTO, and the lower and upper edges indicate the interquartile range (1 st and 3rd quartiles). (**D**) Kaplan-Meier curve illustrating the cumulative incidence of TTO over time, providing a visual representation of the probability of ADE occurrence across different time intervals. ADE: adverse drug event, IQR: interquartile range.

Gastrointestinal disorders

Pemetrexed treatment can induce various gastrointestinal adverse reactions, including nausea, vomiting, diarrhea, decreased appetite, and mucositis/pharyngitis, with a higher incidence observed when combined with cisplatin[30]. Additionally, our study identified rare but severe complications such as esophagitis, colitis, and gastrointestinal bleeding. These adverse reactions may be mediated by multiple mechanisms, including direct cytotoxic effects, folate metabolism disruption, inflammation pathway activation, and gut microbiota dysbiosis. An animal model study revealed that pemetrexed significantly altered gut microbiota composition, increasing the abundance of specific bacterial families (e.g., Enterobacteriaceae and Streptococcaceae) and disrupting epithelial barrier integrity, thereby exacerbating gastrointestinal discomfort[31]. Furthermore, the severity of gastrointestinal adverse reactions varies among individuals. A study analyzing NSCLC patients undergoing pemetrexed treatment found that grade 2 or higher nausea and fatigue significantly increased chemotherapy discontinuation rates, indicating that these symptoms may be key factors affecting treatment adherence[32]. Management strategies typically include symptomatic treatment, such as antiemetics to control nausea, fluid replacement to alleviate constipation, and individualized treatment adjustments or adjunctive therapy to mitigate adverse reactions[33,34]. Additionally, close monitoring of gastrointestinal status and preventive measures such as folic acid and vitamin B12 supplementation can reduce pemetrexed toxicity[6].

Renal and urinary disorders

Our study identified "Renal and urinary disorders" as a significant SOC for pemetrexed-associated AEs. Among these, tubular injury has emerged as a prominent signal for pemetrexed-induced nephrotoxicity. Pemetrexed is primarily excreted via the kidneys, and its accumulation in proximal tubular epithelial cells can lead to acute kidney injury (AKI). Studies have demonstrated that folate receptor alpha (FRα) is highly expressed on the brush border membrane of proximal tubules and is responsible for folate reabsorption, a mechanism that may

render antifolate drugs (such as pemetrexed) nephrotoxic[35]. Additionally, antifolate drugs may further impair renal function by inhibiting folate metabolism enzymes[35]. Other studies have reported rare cases of pemetrexed-induced nephrogenic diabetes insipidus[36]. Mechanistic studies suggest that pemetrexed can increase reactive oxygen species (ROS) levels, impair mitochondrial function, and induce apoptosis[37]. Notably, persistent tubular injury may induce interstitial fibrosis and eventually progress to chronic kidney disease (CKD)[38]. Given the severity of pemetrexed-associated nephrotoxicity, for patients with impaired renal function (eGFR < 45 mL/min), dose adjustments or extended dosing intervals have been suggested to reduce drug accumulation and nephrotoxicity risk[39].

SOCs meeting positive signal thresholds in FAERS only

Infections and infestations

Infectious and pulmonary toxicity induced by pemetrexed pose significant clinical challenges, including risks of infectious pneumonia, sepsis, erysipelas, and interstitial lung disease (ILD). These adverse effects may result from a combination of myelosuppression, immune dysfunction, and direct cytotoxicity on alveolar epithelial cells[40]. Notably, the correlation between pemetrexed and ILD is significant, with a higher incidence of pulmonary toxicity observed in patients with a history of ILD[41]. Disruption of alveolar epithelial integrity and oxidative stress may further exacerbate ILD, manifesting as progressive dyspnea and diffuse lung inflammation[42]. Additionally, pemetrexed affects host immunity by inhibiting folate pathways, leading to decreased natural killer cell activity and weakened defense against bacterial, viral, and fungal infections[43]. Overall, the high risk of pemetrexed-related infections and pulmonary toxicity underscores the need for infection prevention strategies and pulmonary function monitoring to mitigate severe complications.

Cardiac disorders

Although cardiac toxicity associated with pemetrexed is rare, its potential severity cannot be overlooked. Our study found that pemetrexed may lead to pericardial effusion, pericarditis, myocarditis, acute coronary syndrome, and atrial flutter. The underlying mechanisms may involve direct cardiotoxicity, inflammatory responses, oxidative stress, and mitochondrial dysfunction[44]. Cancer therapy has been associated with acute cardiac events such as acute coronary syndrome, myocarditis, QT prolongation, pericardial effusion, and hypotension, with hypersensitivity reactions potentially contributing to coronary artery spasm, acute coronary syndrome (e.g., Kounis syndrome), and cancer therapy-induced myocarditis[45]. Additionally, cardiotoxicity may manifest as dose-dependent myocardial injury, which can persist even after drug discontinuation[46]. As pemetrexed inhibits folate metabolism, it may disrupt myocardial energy metabolism and cellular repair, while chemotherapy-induced inflammatory cytokine release can promote cardiac tissue damage and exacerbate cardiac burden[46,47]. Moreover, chemotherapy-induced endothelial dysfunction may increase thrombotic risk, thereby triggering acute coronary syndrome[48]. Given these potential cardiac risks, careful monitoring and timely management of cardiovascular complications following pemetrexed administration are essential.

Hepatobiliary disorders

Our study revealed that patients receiving pemetrexed treatment exhibited liver function impairment, including hepatitis, hypertransaminasaemia, and cholestasis. These findings suggest that pemetrexed may exert hepatotoxic effects. Studies have shown that pemetrexed-associated liver injury is relatively common but generally manageable and may be correlated with favorable treatment responses[49]. However, the exact mechanisms underlying these toxicities remain unclear. Current research indicates that drug-induced liver injury (DILI) is often associated with oxidative stress damage and immune-mediated inflammatory responses[50]. Additionally, genetic factors may play a role in the occurrence and progression of liver injury. A study identified that the rs1051298 mutation in the SLC19 A1 gene significantly increased the risk of liver damage ($P = 0.0056$, OR = 3.863), suggesting that individual genetic backgrounds may influence patient tolerance to pemetrexed[51]. Therefore, for patients with abnormal liver function or underlying hepatic diseases, close monitoring of liver enzymes is essential to minimize the risk of severe AEs.

Adverse reactions in other SOCs

Based on our disproportionality analysis, ADEs associated with pemetrexed administration may involve multiple organ systems. Metabolic and nutritional disorders related to pemetrexed use observed in our study included dehydration, hypokalaemia, and hyponatraemia. Chemotherapy-induced fluid imbalance and electrolyte disturbances may provide a plausible explanation for these conditions[52,53]. Additionally, chemotherapy-related appetite loss and insufficient nutrient intake may further exacerbate electrolyte imbalances[54].With regard to pemetrexed-associated hypothyroidism, potential mechanisms include immune-mediated thyroid tissue destruction and endocrine dysregulation leading to impaired thyroid hormone synthesis and suppression of the hypothalamic-pituitary-thyroid axis[55,56].Beyond these commonly reported adverse reactions, some less frequently documented toxicities related to the vascular and lymphatic systems warrant caution. Our study identified a significant association between pemetrexed administration and deep vein thrombosis as well as vasculitis. These effects may be linked to chemotherapy-induced hypercoagulability and inflammatory responses. Chemotherapeutic agents can promote vascular endothelial injury, activate the coagulation cascade, and enhance platelet aggregation, thereby increasing the risk of thromboembolic events[57].Regarding pemetrexed-associated skin and subcutaneous tissue disorders, we observed a significant correlation between pemetrexed use and maculopapular rash, skin toxicity, and pseudocellulitis. Chemotherapy agents may compromise skin barrier integrity, predisposing patients to secondary infections and increasing the likelihood of pseudocellulitis[58]. In conclusion, our study identified multiple organ system-related adverse reactions associated with pemetrexed, including metabolic disturbances, endocrine dysfunction, thrombotic events, and skin toxicity. These newly

recognized signals highlight the need for heightened vigilance in clinical practice and pharmacovigilance, as well as the necessity of incorporating these findings into future updates of drug safety guidelines.

Time to onset

The temporal relationship between drug administration and onset of AEs is crucial for evaluating drug safety, as it can help identify specific risk windows and facilitate the prevention or early diagnosis of adverse reactions[59]. TTO analysis demonstrated that most ADEs occurred within the first two months of pemetrexed administration, with a steep decline thereafter. This pattern reflects the acute nature of pemetrexed toxicity and underscores a critical monitoring period early in treatment. The Weibull distribution further confirmed an early failure pattern, suggesting that the risk of ADEs diminishes over time. These findings can inform clinical decision-making regarding follow-up frequency and patient education.

Limitations

Although our study suggests a potential significant relationship between pemetrexed use and ADE reporting in the FAERS and JADER databases, certain limitations must be acknowledged. First, FAERS and JADER are spontaneous reporting systems, and the information collected from various countries and healthcare professionals may be incomplete or inaccurate, potentially introducing bias into the analysis. Second, while we provided a detailed discussion, these databases do not provide sufficient evidence to establish a causal relationship between drug exposure and ADEs[59]. Therefore, our findings should primarily serve as an alert for clinicians and pharmacists to remain vigilant regarding potential AEs. Third, monotherapy is uncommon in cancer treatment. Although pemetrexed was identified as the primary suspect drug in reported ADEs, and we conducted a sensitivity analysis, confirming that pemetrexed alone caused these adverse reactions remains challenging. Finally, this study mainly focused on data from two databases representing the United States and Japan, which may limit the generalizability of the findings to populations with different demographic characteristics, healthcare practices, and prescribing patterns[60]. Considering these limitations is crucial when interpreting our results, and further studies, including clinical trials and self-reported cohort data incorporating clinical dosing information—are encouraged to validate and expand upon our observations.

Conclusion

This study systematically analyzed pemetrexed-associated ADEs using real-world pharmacovigilance data from FAERS and JADER. The findings confirm well-known toxicities, including hematologic, gastrointestinal, and renal disorders, while also identifying novel safety signals, such as cardiac disorders, endocrine dysfunction, and thromboembolic events. TTO analysis revealed that most ADEs occurred within the first two months of treatment, suggesting an early failure pattern for certain toxicities. Given the spontaneous nature of reporting systems, further clinical studies and mechanistic investigations are warranted to validate these findings.

Data availability

This study was conducted using data from the FDA Adverse Event Reporting System (FAERS) and the Japanese Adverse Drug Event Report (JADER) database. Both databases are publicly accessible. FAERS data were obtained from the official website of the U.S. Food and Drug Administration (FDA): http://www.fda.gov/, and JADER data were retrieved from the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan: https://www.pmda.go.jp/index.html.

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Author contributions

L.L. and X.W. designed the study. L.L., X.W., Y.R., and Y.G. collected and curated the data. L.L. and X.W. analyzed the data and generated Figs. 1, 2, 3, 4 and 5; Tables 1, 2, 3 and 4. H.W. and X.L. contributed to data interpretation and provided clinical expertise. L.L. and X.W. wrote the main manuscript text. H.W. and X.L. provided project supervision and funding support. All authors reviewed and approved the final manuscript. L.L. and X.W. contributed equally to this work.

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Declarations

Competing interests

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Conflict of interest

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Additional information

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