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Adverse event profile of crizotinib in real-world from the FAERS database: a 12-year pharmacovigilance study

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Abstract

Aim Crizotinib, an anaplastic lymphoma kinase tyrosine kinase inhibitor (ALK-TKI). It gained approval from the U.S. Food and Drug Administration (FDA) specifically for treating ALK-positive non-small cell lung cancer (NSCLC). The objective of the present investigation was to evaluate adverse events (AEs) associated with crizotinib in real-world by employing data mining on the U.S. FDA Adverse Event Reporting System (FAERS).

Methods Data encompassing AEs linked to crizotinib from 2011 to 2023 were gathered. Disproportionality analyses, which involved the utilization of reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS), were employed for analytical purposes.

Results A total of 10,226 reports documenting crizotinib-associated AEs were extracted from the FAERS database. Out of these, 147 preferred terms (PTs) displaying significant disproportionality were identified concurrently across all four algorithms. The most frequently observed AEs included increased transaminases, bradycardia, prolonged QT, nausea, vomiting, diarrhea, constipation, visual impairment, and interstitial lung disease, which were consistent with previous reports from clinical trials. Additionally, unexpected significant AEs such as deep vein thrombosis, pneumocystis jirovecii pneumonia, gastrointestinal amyloidosis, and hepatic coma were also observed.

Conclusion Crizotinib offers therapeutic benefits but is also accompanied by various risks in the form of AEs. Our study findings align with previous clinical observations, and furthermore, we have identified unforeseen serious AEs. This discovery serves as a novel basis for the monitoring of dosages and the identification of risks associated with crizotinib.

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Keywords Crizotinib, ALK inhibitor, FAERS database, Pharmacovigilance, Adverse events

Introduction

Presently, lung cancer stands as the foremost contributor to cancer-related mortality worldwide among both males and females, constituting approximately 21% of all cancer cases [1]. Non-small cell lung cancer (NSCLC) comprises a substantial majority, ranging from 80 to 85%, of lung cancer cases and serves as the predominant subtype associated with mortality in lung cancer [2]. Approximately 5% of advanced NSCLC has anaplastic lymphoma kinase (ALK) gene rearrangement [3], ALK-tyrosine kinase inhibitors (ALK-TKIs), which include crizotinib, ceritinib, alectinib, brigatinib, and lorlatini, are suitable for individuals diagnosed with ALK-positive NSCLC. Crizotinib, classified as a first-generation ALK-TKI, received regulatory approval from the U.S. Food and Drug Administration (FDA) in August 2011, followed by the European Medicine Agency (EMA) in October 2012, and China in January 2013 [4]. In addition, crizotinib can also be effective in NSCLC patients with ROS1-rearranged, c-MET amplification, and c-MET mutation [5, 6].

The administration of crizotinib to the initial patient diagnosed with advanced ALK-positive NSCLC resulted in a swift amelioration of symptoms [7], promoting large-scale clinical studies' development. Among the 143 patients evaluated in the phase I study, PROFILE 1001, crizotinib demonstrated a consistent alleviation of symptoms in individuals diagnosed with ALK-positive NSCLC, as evidenced by an objective response rate (ORR) of 61% and a median progression-free survival (PFS) of 9.7 months [8]. Similar findings were reported in the phase II study, PROFILE 1005, which focused on previously treated patients with advanced ALK-positive NSCLC [9]. Following the initial study, denoted as PROFILE 1007, a phase III trial was conducted to compare crizotinib, administered as a second-line treatment for advanced/metastatic ALK-positive NSCLC, with standard chemotherapy. The outcomes revealed that the crizotinib arm exhibited a prolonged progression-free survival (PFS) of 4.2 months in contrast to 2.6 months in the standard chemotherapy group, alongside a higher objective response rate (ORR) of 30% versus 9% [10]. Recently, fresh findings stemming from the first-line phase III trial, PROFILE 1014, in ALK-positive NSCLC, demonstrated the superiority of crizotinib over standard chemotherapy, with a median PFS of 10.9 months and an ORR of 74% [11]. The confirmation of crizotinib's remarkable effectiveness and tolerability through these clinical studies has expedited its approval for the treatment of ALK-positive NSCLC. Nonetheless, the limitations inherent in clinical trials fail to capture the full spectrum of adverse events experienced in real-world settings. Consequently, the utilization of data mining algorithms becomes imperative in identifying potential adverse reactions associated with crizotinib within real-world data.

The FDA Adverse Event Reporting System (FAERS) is one of the largest pharmacovigilance databases globally, which serves as a public repository utilized by the U.S. FDA for the collection of post-marketing safety data concerning approved drugs and therapeutic biologics [12]. Through the utilization of data mining techniques, this study conducted a retrospective analysis of crizotinib adverse events in the FDA Adverse Event Reporting System (FAERS) spanning the period from the third quarter of 2011 to the fourth quarter of 2023. The findings of this investigation hold the potential to serve as a valuable point of reference for clinicians, pharmacists, and health policymakers in their efforts to effectively monitor adverse drug reactions and foster the rational utilization of drugs in clinical practice.

Materials and methods

Data sources

Retrospectively obtained from the FAERS, the data utilized in this pharmacovigilance study encompassed diverse categories. These included demographic and administrative information (DEMO), drug-related details (DRUG), reported adverse events (REAC), patient outcomes (OUTC), reporting sources (RPSR), initiation and cessation dates of drug therapy (THER), indications (INDI), as well as deleted cases. To retrieve the report data from FAERS, the keyword "crizotinib" was employed. The study period spanned from the third quarter of 2011 to the fourth quarter of 2023, with reporters consisting of physicians, pharmacists, other healthcare professionals, and consumers.

Data extraction and analysis

We obtained the crizotinib report from the FAERS database, and the detailed screening process is shown in Fig. 1. Duplicate reports identified based on the same case ID were removed, and only reports with the latest date could be retained. After importing the data into MYSQL software and matching the DRUG data with "crizotinib" as the drug name, reports that qualified the primary suspected (PS) drug as crizotinib were extracted. These reports encompassed a variety of information, including indications, outcome events, incidence, onset time of events, clinical characteristics, the reporter and the region, reporting date, and occurrence time to medication date. For analysis purposes, AEs underwent standardization and categorization utilizing the International Medical Dictionary for Regular Activities (MedDRA).

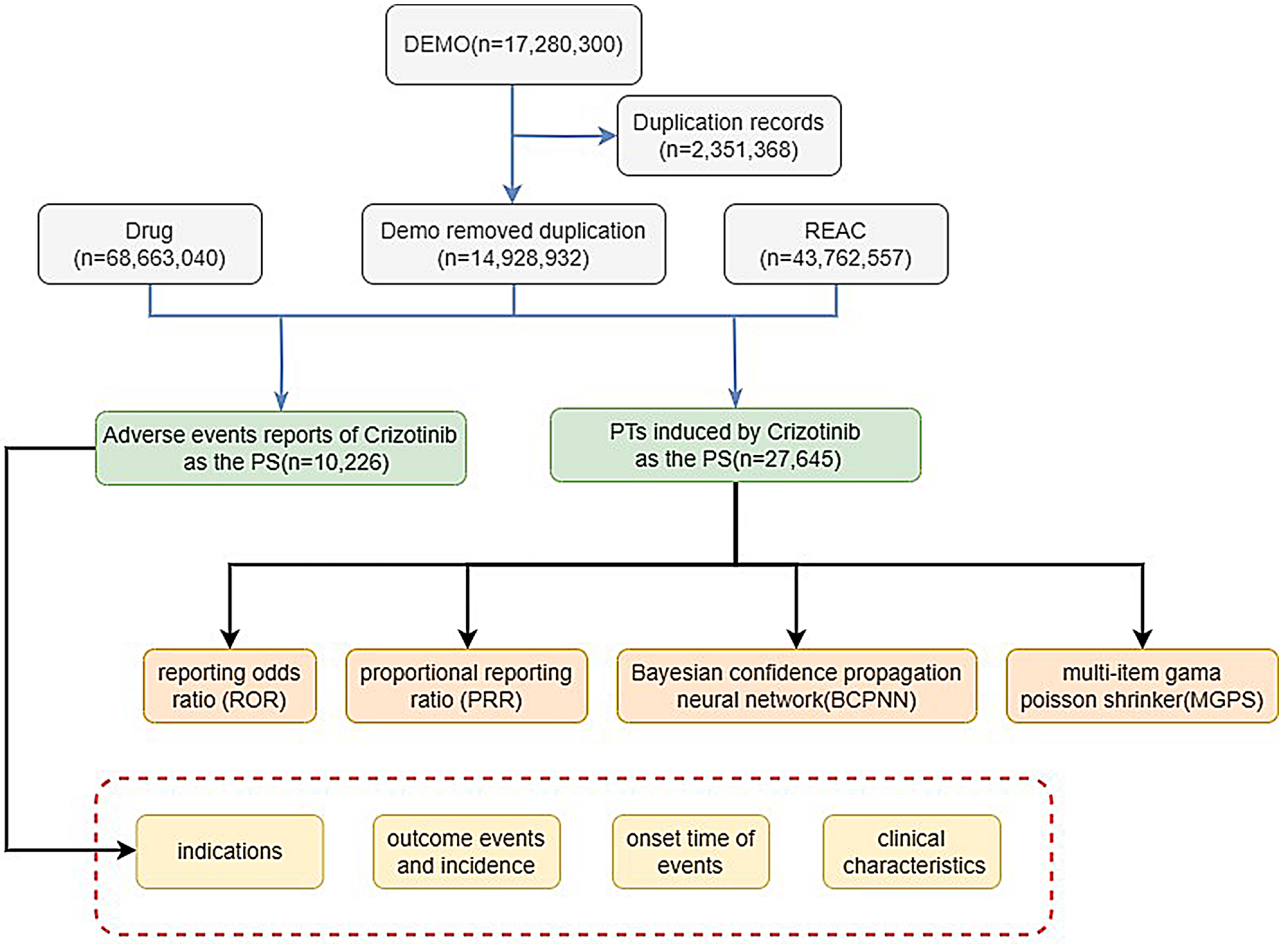

Fig. 1 The flow diagram of selecting crizotinib-related AEs from FAERS database

This involved the classification of AEs into system organ classes (SOC) and preferred terms (PT). Both SOC and PT were employed in the analysis process.

In our investigation, the identification of potential signals between crizotinib and all AEs was accomplished through the application of disproportionality analysis. To detect associations between crizotinib and AE signals, reporting odds ratios (ROR) [13], proportional reporting ratios (PRR) [14], Bayesian confidence propagation neural network (BCPNN) [15], and multi-item gamma Poisson shrinker (MGPS) [16] were calculated using established formulas. The MGPS method employs an empirical Bayesian model that calculates an adjusted ratio of observed values to expected values, known as the empirical Bayesian geometric mean (EBGM). Cross-validation of four algorithms reduces false positive rates and helps detect rare adverse reactions. Algorithms of the four primary methods are shown in a four-cell table (Table 1). One signal is considered to have been generated when the intensity of the target event occurring for the target drug is above the set threshold and its frequency had to surpass the background frequency within the database. The strength of the signal was determined by the magnitude of this value, indicating a more pronounced statistical association between the target drug and the target AE. Statistical analysis was conducted utilizing MYSQL 8.0 and Microsoft Excel 2021 software.

Results

Basic characteristics of crizotinib-related AEs

From the third quarter of 2011 to the fourth quarter of 2023, the FAERS database received 17,280,300 AE reports. Among these, 10,226 reports where crizotinib was identified as the primary suspect (PS) drug for AEs were reported. The basic information of reports with crizotinib is presented in Table 2. This report showed slightly more female patients than male patients (49.34% vs. 39.81%). The median age of the patients was 63 years, and the largest percentage of patients aged 45–65 years was reported (30.16%). More than half of the reports were submitted by health professionals, including physicians (36.49%), pharmacists (14.31%), and other health professionals (15.62%). Notably, 32.53% of reports came from consumers. The country that reported the most

Table 1 Algorithms, equations, and thresholds of the four primary methods

Algorithms	Equation	Threshold
ROR	$ROR = \frac{ad}{bc}$	$N \geq 3$, lower limit of 95% CI > 1
	$SE\left(\ln ROR\right) = \sqrt{\left(\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}\right)}$	
	$95\%\ CI = e^{\ln \mathrm{ROR} \pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$	
PRR	$PRR = \frac{a/(a+b)}{c/(c+d)}$	$N \geq 3$, lower limit of 95% CI > 1, $\chi^2 \geq 4$
	$SE(\ln PRR) = \sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}$	
	$95\%\ CI = e^{\ln(PRR) \pm 1.96\sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}}$	
	$\chi^2 = \left[(\text{ad-}bc)\text{^}2\right](a+b+c+d) / [(a+b)(c+d)(a+c)(b+d)]$	
BCPNN	$IC = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$	IC025 > 0
	$\gamma = \gamma 11 \frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$	
	$E(IC) = \log_2 \frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$	
	$V(IC) = \frac{1}{(\ln 2)^2}\left\{\left[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}\right] + \left[\frac{(a+b+c+d)-(a+b)+a-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}\right] + \left[\frac{(a+b+c+d)-(a+c)+\beta-\beta 1}{(a+c+\beta 1)(1+a+b+c+d+\beta 1)}\right]\right\}$	
	$95\%CI = E(IC) \pm 2V(IC)\text{^}0.5$	
EBGM	$EBGM = \frac{a(a+b+c+d)}{(a+c)(a+b)}$	EBGM05>2
	$95\%CI = e^{\ln(EBGM) \pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$	

Notes Equation: a, number of reports containing crizotinib-related AEs of crizotinib; b, number of reports containing non-crizotinib-related AEs of the crizotinib; c, number of reports containing the crizotinib-related AEs of other drugs; d, number of reports containing non-crizotinib-related AEs of other drugs

Abbreviations N case reports, *95% CI* 95% confidence interval, *χ^2* chi-squared, *IC* information component, *IC025* the lower limit of 95% CI of the IC, *E(IC)* the IC expectations, *V(IC)* the variance of IC, *EBGM* empirical Bayesian geometric mean, *EBGM05* the lower limit of 95% CI of EBGM

was the United States, accounting for 51.20% of the total, followed by India (7.82%), Japan (7.68%), China (3.80%), and France (3.53%), respectively. The most reported year was 2014 (11.53%), followed by 2015 (10.84%), 2016 (10.59%), 2013 (9.54%), 2019 (8.91%), 2017 (8.60%), and 2018 (8.42%), respectively. In terms of severe outcomes, the most frequently reported is death (37.80%), followed by other severe (32.49%) and hospitalization (25.93%) events. The median onset time of crizotinib-related AEs was 41.00 days (12.00, 154.75). Unfortunately, 56.59% of the onset times are unknown, which may lead to inaccuracies in the median onset time.

Crizotinib signal detection

In this analysis, AEs reports of crizotinib at the SOC level amounted to 24 items, and details are shown in Table 3. The signals that simultaneously met all of the above four algorithm standards were "neoplasms benign, malignant and unspecified (incl cysts and polyps) (n = 2329, ROR 3.04, PRR 2.86, IC 1.52, EBGM 2.86)" and "hepatobiliary disorders (n = 524, ROR 2.21, PRR 2.19, IC 1.13, EBGM 2.19)". The signal detections of "eye disorders (n = 1098, ROR 2, PRR 1.96, IC 0.97, EBGM 1.96)", "gastrointestinal disorders (n = 4015, ROR 1.79, PRR 1.67, IC 0.74, EBGM 1.67)", "respiratory, thoracic and mediastinal disorders (n = 2072, ROR 1.59, PRR 1.55, IC 0.63, EBGM 1.55)", "metabolism and nutrition disorders (n = 820, ROR 1.4, PRR 1.39, IC 0.48, EBGM 1.39)", "investigations (n = 2151, ROR 1.32, PRR 1.3, IC 0.38, EBGM 1.3)" and "general disorders and administration site conditions (n = 6195, ROR 1.29, PRR 1.22, IC 0.29, EBGM 1.22)" were positive with ROR, PRR and IC methods while not with EBGM, suggesting these signals might also be essential and frequent.

After excluding neoplasms benign, malignant, and unspecified (including cysts and polyps), which may be caused by disease progression, a total of 147 significant PTs of interest conforming to all four algorithms simultaneously are described in Table 4. In this study, transaminases increased, electrocardiogram QT prolonged, nausea, visual impairment, and other AEs were present, which consistent with the medication warnings and side effects reported in previous clinical trials. Interestingly, unexpected significant AEs marked with * in PTs lists, including liver abscess, pneumocystis jirovecii pneumonia, oesophageal candidiasis, gastrointestinal amyloidosis, and so on, were uncovered in the label. Although there were few cases, the signal strength of the unreported side effects was strong. Events have been reported

Table 2 Basic information of reports with crizotinib on AEs from the FAERS database

Characteristics	Case number, *n*	Case proportion, %
Number of events	10,226	
Gender		
Female	5045	49.34
Male	4071	39.81
Unknown	1110	10.85
Age		
<18	200	1.96
18 ~ 45	963	9.42
45 ~ 65	3084	30.16
65 ~ 75	2010	19.66
>=75	1440	14.08
Unknown	2529	24.73
Reporter		
Physician	3731	36.49
Consumer	3327	32.53
Other health-professional	1597	15.62
Pharmacist	1463	14.31
Unknown	108	1.06
Reported countries		
United States	5236	51.20
other	1294	12.65
India	800	7.82
Japan	785	7.68
China	389	3.80
France	361	3.53
Canada	192	1.88
United Kingdom	182	1.78
Argentina	165	1.61
Germany	131	1.28
Italy	117	1.14
Korea, South	112	1.10
Colombia	82	0.80
Australia	81	0.79
Taiwan	65	0.64
Netherlands	62	0.61
Thailand	62	0.61
Turkey	59	0.58
Brazil	51	0.50
Report year		
2011	76	0.74
2012	620	6.06
2013	976	9.54
2014	1179	11.53
2015	1108	10.84
2016	1083	10.59
2017	879	8.60
2018	861	8.42
2019	911	8.91
2020	721	7.05
2021	645	6.31
2022	574	5.61
2023	593	5.80
Severe outcomes		
Death	3347	37.80
Other serious	2877	32.49
Hospitalization	2296	25.93
Life threatening	250	2.82
Disability	79	0.89
Required intervention to prevent permanent impairment/damage	5	0.06
Time to onset (days)		
< 7	487	7.57
7 ~ 28	665	10.33
28 ~ 56	423	6.57
>=56	1219	18.94
Unknown	3643	56.59

in patients treated with crizotinib in previous clinical studies, such as gastrointestinal perforation, hypogonadism, anaemia, ventricular arrhythmia, septic shock, sepsis, and diabetic ketoacidosis. However, they did not meet the criteria for our analysis's four algorithms.

Discussion

With the development of precision medicine, targeted therapy for lung cancer has been developing rapidly over the years. Crizotinib, the earliest approved ALK inhibitor, has been on the market for 12 years. However, the majority of research concerning the adverse reactions of crizotinib has predominantly concentrated on clinical trials and case reports. While there exist studies that synthesize the adverse reactions of various ALK inhibitors, including crizotinib and alectinib, as documented in the FAERS database [17] to date, no distinct reports specifically addressing the adverse reactions of crizotinib alone have been identified within the FAERS database. We collected and updated the adverse drug reactions of crizotinib from the FAERS database. The primary objective of this investigation is to evaluate the post-marketing safety of crizotinib and generate more precise evidence to support the rational utilization of this medication in clinical practice.

As we can notice from Table 2, AEs of crizotinib were more prevalent in females (49.34%) than males (39.81%), which may be related to the fact that non-smoking female lung cancer patients are more likely to have an ALK gene rearrangement [18], resulting in an increased chance of medication administration. More than half (66.42%) of the reports were from health professionals, suggesting that the source of reporting information was reliable. The use of crizotinib showed a downward trend year by year from 2014 to 2018, possibly due to the launch of second and third-generation ALK inhibitors.

Table 3 The signal strength of AEs of crizotinib at the SOC level in the FAERS database

SOC	Case reports	ROR (95%CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2329**	**3.04 (2.91, 3.17)**	**2.86 (2.75, 2.97)**	**2906.51**	**1.52 (1.46)**	**2.86 2.76)**
Hepatobiliary disorders	**524**	**2.21 (2.03, 2.41)**	**2.19 (2.02, 2.37)**	**340.28**	**1.13 (1)**	**2.19 (2.03)**
Eye disorders	**1098**	**2 (1.88, 2.12)**	**1.96 (1.85, 2.08)**	**524.63**	**0.97 (0.88)**	**1.96 (1.86)**
Gastrointestinal disorders	**4015**	**1.79 (1.73, 1.85)**	**1.67 (1.64, 1.7)**	**1192.01**	**0.74 (0.69)**	**1.67 (1.63)**
Respiratory, thoracic and mediastinal disorders	**2072**	**1.59 (1.52, 1.67)**	**1.55 (1.49, 1.61)**	**421.17**	**0.63 (0.56)**	**1.55 (1.49)**
Metabolism and nutrition disorders	**820**	**1.4 (1.31, 1.5)**	**1.39 (1.31, 1.47)**	**91.87**	**0.48 (0.38)**	**1.39 (1.31)**
Investigations	**2151**	**1.32 (1.27, 1.38)**	**1.3 (1.25, 1.35)**	**157.33**	**0.38 (0.31)**	**1.3 (1.25)**
General disorders and administration site conditions	**6195**	**1.29 (1.25, 1.32)**	**1.22 (1.2, 1.24)**	**304.02**	**0.29 (0.25)**	**1.22 (1.19)**
Ear and labyrinth disorders	129	1.05 (0.88, 1.25)	1.05 (0.88, 1.25)	0.31	0.07 (-0.18)	1.05 (0.91)
Cardiac disorders	695	1.03 (0.96, 1.11)	1.03 (0.95, 1.11)	0.63	0.04 (-0.07)	1.03 (0.97)
Renal and urinary disorders	530	0.99 (0.91, 1.08)	0.99 (0.92, 1.07)	0.06	-0.02 (-0.14)	0.99 (0.92)
Blood and lymphatic system disorders	439	0.94 (0.85, 1.03)	0.94 (0.85, 1.04)	1.81	-0.09 (-0.23)	0.94 (0.87)
Infections and infestations	1259	0.82 (0.78, 0.87)	0.83 (0.78, 0.88)	46.99	-0.27 (-0.35)	0.83 (0.79)
Vascular disorders	481	0.82 (0.75, 0.89)	0.82 (0.74, 0.9)	19.43	-0.29 (-0.42)	0.82 (0.76)
Nervous system disorders	1729	0.73 (0.69, 0.76)	0.74 (0.71, 0.77)	165.98	-0.43 (-0.5)	0.74 (0.71)
Endocrine disorders	44	0.61 (0.45, 0.82)	0.61 (0.45, 0.82)	10.9	-0.71 (-1.13)	0.61 (0.48)
Musculoskeletal and connective tissue disorders	639	0.41 (0.38, 0.44)	0.42 (0.39, 0.45)	542.77	-1.25 (-1.36)	0.42 (0.39)
Injury, poisoning and procedural complications	1010	0.33 (0.31, 0.36)	0.36 (0.34, 0.38)	1288.3	-1.48 (-1.57)	0.36 (0.34)
Skin and subcutaneous tissue disorders	512	0.31 (0.29, 0.34)	0.33 (0.31, 0.36)	748.16	-1.61 (-1.73)	0.33 (0.3)
Psychiatric disorders	406	0.25 (0.22, 0.27)	0.26 (0.24, 0.29)	914.43	-1.95 (-2.09)	0.26 (0.24)
Congenital, familial and genetic disorders	17	0.2 (0.12, 0.32)	0.2 (0.12, 0.32)	54.29	-2.32 (-2.98)	0.2 (0.13)
Reproductive system and breast disorders	41	0.18 (0.13, 0.24)	0.18 (0.13, 0.25)	156.05	-2.48 (-2.92)	0.18 (0.14)
Immune system disorders	56	0.17 (0.13, 0.22)	0.17 (0.13, 0.22)	226.91	-2.54 (-2.92)	0.17 (0.14)
Pregnancy, puerperium and perinatal conditions	5	0.04 (0.02, 0.1)	0.04 (0.02, 0.1)	106.68	-4.54 (-5.69)	0.04 (0.02)

Notes Bold indicates a positive signal defined as at least one of the four algorithms that meet the criteria

Abbreviations SOC System Organ Class, *ROR* reporting odds ratio, *CI* confidence interval, *PRR* proportional reporting ratio, *χ2* chi-squared, *IC* information component, *EBGM* empirical Bayesian geometric mean

According to the results of disproportionality analysis, the most frequently reported and significant signals at the SOC level were "neoplasms benign, malignant and unspecified (incl cysts and polyps)", which included "lung adenocarcinoma, non-small cell lung cancer, lung cancer metastatic, tracheal cancer, bronchial cancer, neoplasm recurrence" marked with † in Table 4, those had not been reported in clinical studies related to crizotinib, and most likely due to disease progression of cancer patients rather than crizotinib treatment. According to the literature, the most common metastatic sites of lung cancer include the nervous system (39%), bone (34%), liver (20%), respiratory system (18%) and adrenal gland (8%) [19]. Therefore, The AEs at PTs level such as disease progression, carcinoembryonic antigen increased, blood lactate dehydrogenase increased, pleural thickening, haemoptysis, brain oedema, hydrothorax, pleural effusion may also be related to tumour progression rather than caused by crizotinib. Death accounted for 37.80% of serious outcome events due to adverse reactions, which we also believe may be related to tumour progression.

According to previous literature, visual impairment was the most common adverse reaction (41-73%) of crizotinib in clinical trials [8–11, 20]. As shown in the "eye disorder" subsection of Table 4, the visual impairment included blurred vision, vitreous fiducials, diplopia, and photophobia, which were shown to have strong signals in the report of this study. Notably, the newly identified AEs, including halo vision, amaurosis, and visual field defect, showed strong signals, and this is worth further attention from physicians and pharmacists to the AEs of visual impairment caused by crizotinib. Although visual impairment caused by crizotinib is usually grade 1–2, it does not affect the patient's quality of life and does not require intervention therapy. However, the administration of crizotinib may interfere with daily tasks for patients such as drivers and pilots. Therefore, clinicians should discuss the risk of visual impairment with patients in advance and perform ophthalmological or optic-neurological

Table 4 The signal strength of AEs of crizotinib at the PTs level in the FAERS database

SOC	PTs	Case reports	ROR (95%CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
Eye disorders	Photopsia	127	46.2 (38.71, 55.14)	45.99 (38.55, 54.86)	5425.75	5.48 (5.23)	44.67 (38.52)
	Visual brightness*	7	44.46 (20.97, 94.28)	44.45 (21.11, 93.61)	288.86	5.43 (4.42)	43.21 (23.04)
	Vitreous floaters	74	16.91 (13.44, 21.27)	16.86 (13.33, 21.33)	1092.31	4.06 (3.73)	16.69 (13.77)
	Halo vision*	6	12 (5.37, 26.8)	12 (5.37, 26.8)	60.01	3.57 (2.5)	11.91 (6.08)
	Amaurosis*	3	8.91 (2.86, 27.72)	8.91 (2.86, 27.77)	20.94	3.15 (1.73)	8.86 (3.43)
	Visual field defect*	27	8.76 (6, 12.79)	8.75 (6.03, 12.7)	184.4	3.12 (2.59)	8.71 (6.35)
	Ocular toxicity	3	7.54 (2.42, 23.44)	7.54 (2.42, 23.5)	16.93	2.91 (1.49)	7.51 (2.91)
	Visual impairment	367	6.19 (5.58, 6.86)	6.12 (5.55, 6.75)	1568.86	2.61 (2.46)	6.1 (5.59)
	Optic neuropathy	4	4.73 (1.77, 12.62)	4.73 (1.78, 12.6)	11.72	2.24 (0.97)	4.72 (2.07)
	Photophobia*	37	4.46 (3.23, 6.16)	4.46 (3.26, 6.1)	98.93	2.15 (1.69)	4.45 (3.39)
	Diplopia	44	4 (2.97, 5.38)	3.99 (2.97, 5.35)	98.53	1.99 (1.57)	3.99 (3.11)
	Vision blurred	148	2.47 (2.1, 2.9)	2.46 (2.1, 2.88)	127.97	1.3 (1.06)	2.45 (2.14)
Gastrointestinal disorders	Gastrointestinal amyloidosis*	3	91.07 (28.4, 292)	91.06 (28.65, 289.43)	252.09	6.43 (4.96)	85.96 (32.43)
	Oesophagitis ulcerative	7	29.35 (13.89, 62.02)	29.35 (13.94, 61.81)	188.04	4.85 (3.84)	28.81 (15.41)
	Necrotising oesophagitis	5	24.97 (10.32, 60.42)	24.96 (10.33, 60.3)	113.15	4.62 (3.45)	24.57 (11.73)
	Oesophageal ulcer	32	19.72 (13.91, 27.95)	19.69 (13.84, 28.02)	560.6	4.28 (3.79)	19.45 (14.53)
	Oesophagitis	78	18.26 (14.6, 22.83)	18.21 (14.68, 22.59)	1253.79	4.17 (3.85)	18.01 (14.93)
	Oesophageal pain	22	12.87 (8.46, 19.59)	12.86 (8.52, 19.41)	238.66	3.67 (3.08)	12.76 (8.98)
	Oesophageal discomfort	3	10.12 (3.25, 31.5)	10.12 (3.25, 31.54)	24.49	3.33 (1.91)	10.06 (3.89)
	Erosive oesophagitis	6	8.36 (3.75, 18.64)	8.35 (3.74, 18.65)	38.63	3.06 (1.98)	8.31 (4.25)
	Oesophageal spasm	5	6.29 (2.61, 15.15)	6.29 (2.6, 15.19)	22.16	2.65 (1.49)	6.27 (3.01)
	Odynophagia	15	5.95 (3.58, 9.89)	5.95 (3.57, 9.9)	61.54	2.57 (1.86)	5.93 (3.88)
	Oesophageal disorder	10	5.92 (3.18, 11.01)	5.92 (3.16, 11.08)	40.7	2.56 (1.71)	5.9 (3.51)
	Oesophageal stenosis	7	5.75 (2.74, 12.07)	5.75 (2.73, 12.11)	27.34	2.52 (1.52)	5.73 (3.08)
	Reflux gastritis*	3	5.43 (1.75, 16.88)	5.43 (1.74, 16.92)	10.81	2.44 (1.02)	5.42 (2.1)
	Gastrointestinal toxicity	11	5.39 (2.98, 9.75)	5.39 (2.99, 9.7)	39.18	2.43 (1.61)	5.37 (3.27)
	Pneumoperitoneum*	4	4.84 (1.81, 12.92)	4.84 (1.82, 12.9)	12.15	2.27 (1)	4.83 (2.12)
	Gastrointestinal oedema*	4	4.83 (1.81, 12.9)	4.83 (1.81, 12.87)	12.12	2.27 (1)	4.82 (2.12)
	Dysphagia	168	3.95 (3.4, 4.6)	3.94 (3.37, 4.61)	367.46	1.97 (1.76)	3.93 (3.46)
	Constipation	348	3.58 (3.22, 3.98)	3.55 (3.22, 3.92)	637.11	1.82 (1.67)	3.54 (3.24)
	Vomiting	605	2.95 (2.72, 3.2)	2.91 (2.69, 3.15)	761.45	1.54 (1.42)	2.9 (2.71)
	Nausea	899	2.55 (2.39, 2.73)	2.5 (2.36, 2.65)	820.54	1.32 (1.23)	2.5 (2.36)
	Dyspepsia	107	2.44 (2.02, 2.95)	2.43 (2, 2.96)	90.22	1.28 (1.01)	2.43 (2.07)
	Diarrhoea	660	2.2 (2.03, 2.37)	2.17 (2.01, 2.35)	418.63	1.11 (1)	2.16 (2.03)
Cardiac disorders	Pericardial effusion*	89	8.83 (7.17, 10.88)	8.81 (7.1, 10.93)	612.71	3.13 (2.83)	8.76 (7.36)
	Cardiac fibrillation*	4	6.34 (2.38, 16.94)	6.34 (2.38, 16.89)	17.93	2.66 (1.39)	6.32 (2.78)
	Sinus bradycardia	26	6.33 (4.31, 9.31)	6.33 (4.28, 9.37)	116.11	2.66 (2.11)	6.3 (4.57)
	Cardiopulmonary failure	9	5.31 (2.76, 10.23)	5.31 (2.78, 10.14)	31.4	2.41 (1.51)	5.3 (3.06)
	Bradycardia	95	4.04 (3.3, 4.94)	4.02 (3.3, 4.89)	215.57	2.01 (1.72)	4.02 (3.39)
	Cardiac failure	97	2.66 (2.18, 3.25)	2.66 (2.19, 3.24)	100.07	1.41 (1.12)	2.65 (2.24)
Hepatobiliary disorders	Hepatitis fulminant*	11	9.59 (5.3, 17.36)	9.59 (5.33, 17.27)	84.1	3.25 (2.43)	9.54 (5.81)
	Hypertransaminasaemia	16	5.93 (3.63, 9.68)	5.92 (3.63, 9.66)	65.22	2.56 (1.87)	5.9 (3.91)
	Hepatic function abnormal	90	5.88 (4.78, 7.24)	5.87 (4.73, 7.28)	362.32	2.55 (2.25)	5.85 (4.92)
	Hepatitis	53	5.22 (3.99, 6.84)	5.21 (3.96, 6.86)	179.96	2.38 (1.99)	5.2 (4.15)
	Hepatitis acute	13	4.94 (2.87, 8.52)	4.94 (2.85, 8.55)	40.69	2.3 (1.54)	4.92 (3.12)
	Hepatotoxicity	48	4.88 (3.67, 6.48)	4.87 (3.7, 6.41)	147.27	2.28 (1.88)	4.86 (3.83)
	Hepatic cyst*	7	4.7 (2.24, 9.88)	4.7 (2.23, 9.9)	20.35	2.23 (1.23)	4.69 (2.52)
	Hepatocellular injury	25	3.15 (2.12, 4.66)	3.14 (2.12, 4.65)	36.47	1.65 (1.09)	3.14 (2.26)
	Liver disorder	54	2.87 (2.19, 3.74)	2.86 (2.17, 3.76)	65.38	1.52 (1.13)	2.86 (2.29)

Table 4 (continued)

SOC	PTs	Case reports	ROR (95%CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
Respiratory, thoracic and mediastinal disorders	Pleural thickening*†	8	23 (11.44, 46.24)	23 (11.36, 46.58)	165.8	4.5 (3.55)	22.67 (12.64)
	Hydrothorax*†	9	22.04 (11.41, 42.56)	22.03 (11.31, 42.9)	178.11	4.44 (3.54)	21.73 (12.53)
	Pulmonary artery thrombosis*	7	21.04 (9.98, 44.37)	21.04 (9.99, 44.31)	131.77	4.38 (3.37)	20.76 (11.12)
	Alveolitis	6	10.63 (4.76, 23.72)	10.63 (4.76, 23.74)	51.96	3.4 (2.33)	10.56 (5.39)
	Pneumonitis	113	9.41 (7.82, 11.33)	9.38 (7.86, 11.19)	840.91	3.22 (2.96)	9.33 (7.99)
	Pleural effusion*†	221	8.26 (7.23, 9.43)	8.2 (7.15, 9.41)	1391.66	3.03 (2.84)	8.16 (7.31)
	Vocal cord disorder*	6	6.62 (2.97, 14.77)	6.62 (2.96, 14.79)	28.52	2.72 (1.65)	6.6 (3.37)
	Interstitial lung disease	137	6.51 (5.5, 7.7)	6.48 (5.43, 7.73)	632.81	2.69 (2.45)	6.46 (5.61)
	Diffuse alveolar damage*	3	6.43 (2.07, 19.99)	6.43 (2.06, 20.04)	13.7	2.68 (1.26)	6.41 (2.48)
	Pleurisy*	11	4.19 (2.32, 7.57)	4.19 (2.33, 7.54)	26.61	2.06 (1.24)	4.18 (2.55)
	Pulmonary oedema	78	3.94 (3.15, 4.92)	3.93 (3.17, 4.88)	170.04	1.97 (1.65)	3.92 (3.26)
	Haemoptysis*†	45	3.46 (2.58, 4.64)	3.46 (2.58, 4.64)	78.49	1.79 (1.37)	3.45 (2.7)
	Pulmonary thrombosis	18	3.45 (2.17, 5.48)	3.45 (2.16, 5.52)	31.23	1.78 (1.13)	3.44 (2.34)
	Pulmonary embolism	143	3.37 (2.86, 3.98)	3.36 (2.87, 3.93)	237.07	1.75 (1.51)	3.36 (2.92)
	Hypoxia	47	3.1 (2.33, 4.13)	3.1 (2.31, 4.16)	66.69	1.63 (1.22)	3.09 (2.43)
	Respiratory failure	85	2.69 (2.18, 3.33)	2.69 (2.17, 3.34)	90.11	1.43 (1.12)	2.69 (2.25)
Vascular disorders	Embolism	31	8.42 (5.91, 11.98)	8.41 (5.91, 11.97)	201.23	3.06 (2.56)	8.37 (6.23)
	Venous thrombosis limb*	6	6 (2.69, 13.37)	5.99 (2.68, 13.38)	24.87	2.58 (1.51)	5.98 (3.05)
	Subclavian vein thrombosis*	3	5.97 (1.92, 18.55)	5.97 (1.92, 18.61)	12.36	2.57 (1.15)	5.95 (2.3)
	Deep vein thrombosis*	87	2.9 (2.35, 3.59)	2.9 (2.34, 3.6)	108.09	1.53 (1.23)	2.89 (2.43)
Infections and infestations	Renal cyst infection	12	182.2 (100.1, 331.63)	182.12 (99.19, 334.38)	1929.96	7.35 (6.52)	162.72 (98.58)
	Renal abscess	41	133.16 (96.75, 183.28)	132.96 (97.17, 181.93)	4937.22	6.93 (6.48)	122.33 (93.64)
	Perinephric abscess*	3	46.47 (14.73, 146.58)	46.46 (14.62, 147.67)	129.48	5.5 (4.05)	45.11 (17.25)
	Oesophageal infection*	4	18.97 (7.08, 50.87)	18.97 (7.12, 50.54)	67.26	4.23 (2.95)	18.75 (8.22)
	Fungal oesophagitis*	5	15.78 (6.54, 38.09)	15.78 (6.53, 38.12)	68.49	3.97 (2.8)	15.62 (7.47)
	Psoas abscess*	4	15.22 (5.68, 40.75)	15.21 (5.71, 40.53)	52.6	3.91 (2.64)	15.07 (6.61)
	Muscle abscess*	4	14.7 (5.49, 39.36)	14.7 (5.52, 39.17)	50.58	3.86 (2.59)	14.57 (6.39)
	Oesophageal candidiasis*	20	12.2 (7.85, 18.94)	12.19 (7.92, 18.76)	203.82	3.6 (2.98)	12.1 (8.37)
	Liver abscess*	9	6.2 (3.22, 11.93)	6.2 (3.25, 11.84)	39.07	2.63 (1.73)	6.18 (3.57)
	infectious pleural effusion*	4	5.51 (2.06, 14.71)	5.51 (2.07, 14.68)	14.71	2.46 (1.19)	5.49 (2.42)
	Erysipelas*	9	3.74 (1.95, 7.2)	3.74 (1.96, 7.14)	18.05	1.9 (1.01)	3.74 (2.16)
	Pneumocystis jirovecii pneumonia*	16	3.18 (1.95, 5.2)	3.18 (1.95, 5.19)	23.88	1.67 (0.98)	3.18 (2.11)

Table 4 (continued)

SOC	PTs	Case reports	ROR (95%CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
Investigations	Alpha hydroxybutyrate dehydrogenase Increased*	3	113.84 (35.21, 368.02)	113.83 (35.12, 368.97)	312.1	6.73 (5.25)	105.96 (39.7)
	Albumin globulin ratio decreased*	3	35.85 (11.41, 112.67)	35.85 (11.5, 111.74)	99.29	5.13 (3.7)	35.05 (13.45)
	Carcinoembryonic antigen increased*†	21	24.33 (15.81, 37.45)	24.31 (15.79, 37.42)	462.01	4.58 (3.97)	23.94 (16.69)
	Globulins increased*	3	20.42 (6.54, 63.8)	20.42 (6.55, 63.64)	54.66	4.33 (2.91)	20.16 (7.77)
	Electrocardiogram qt interval abnormal	4	20.24 (7.55, 54.28)	20.24 (7.6, 53.93)	72.18	4.32 (3.05)	19.98 (8.75)
	Blood bilirubin decreased*	4	14.15 (5.29, 37.88)	14.15 (5.31, 37.7)	48.44	3.81 (2.54)	14.03 (6.16)
	Myocardial necrosis marker increased*	10	13.16 (7.06, 24.52)	13.15 (7.02, 24.62)	111.31	3.71 (2.85)	13.05 (7.75)
	Blood albumin decreased	31	10.88 (7.64, 15.49)	10.87 (7.64, 15.47)	275.75	3.43 (2.93)	10.8 (8.03)
	Protein total decreased*	15	10.39 (6.25, 17.27)	10.39 (6.24, 17.3)	126.37	3.37 (2.66)	10.32 (6.75)
	Lymphocyte percentage decreased	4	7.38 (2.76, 19.7)	7.38 (2.77, 19.66)	21.94	2.88 (1.61)	7.35 (3.23)
	Blood chloride increased*	4	6.86 (2.57, 18.32)	6.86 (2.57, 18.28)	19.93	2.77 (1.5)	6.83 (3)
	Granulocyte count decreased	3	5.76 (1.85, 17.89)	5.76 (1.85, 17.95)	11.75	2.52 (1.1)	5.74 (2.22)
	Transaminases increased	58	5.69 (4.4, 7.37)	5.68 (4.4, 7.33)	223.16	2.5 (2.13)	5.67 (4.57)
	Liver function test abnormal	65	5.67 (4.44, 7.23)	5.66 (4.47, 7.16)	248.43	2.5 (2.15)	5.64 (4.6)
	Alanine aminotransferase increased	128	5.52 (4.64, 6.57)	5.5 (4.61, 6.56)	470.14	2.46 (2.21)	5.49 (4.74)
	Liver function test increased	56	5.43 (4.18, 7.06)	5.42 (4.2, 6.99)	201.32	2.43 (2.06)	5.41 (4.34)
	Aspartate aminotransferase increased	102	5.31 (4.37, 6.45)	5.29 (4.35, 6.44)	353.79	2.4 (2.12)	5.27 (4.48)
	Blood alkaline phosphatase increased	43	4.82 (3.57, 6.51)	4.82 (3.59, 6.47)	129.69	2.26 (1.84)	4.8 (3.74)
	Blood sodium increased*	5	4.62 (1.92, 11.13)	4.62 (1.91, 11.16)	14.16	2.21 (1.05)	4.61 (2.21)
	Red cell distribution width increased*	9	4.38 (2.28, 8.44)	4.38 (2.29, 8.36)	23.44	2.13 (1.23)	4.37 (2.53)
	Hepatic enzyme abnormal	9	3.86 (2.01, 7.43)	3.86 (2.02, 7.37)	19.04	1.95 (1.05)	3.85 (2.23)
	Electrocardiogram qt prolonged	63	3.8 (2.97, 4.87)	3.79 (2.94, 4.89)	129.28	1.92 (1.57)	3.79 (3.08)
	Hepatic enzyme increased	111	3.76 (3.12, 4.54)	3.75 (3.14, 4.47)	223.71	1.9 (1.64)	3.74 (3.2)
	Heart rate decreased	62	3.66 (2.85, 4.69)	3.65 (2.83, 4.71)	119.06	1.87 (1.51)	3.64 (2.96)
	Blood creatinine increased	100	3.59 (2.95, 4.37)	3.58 (2.94, 4.36)	185.39	1.84 (1.55)	3.57 (3.03)
	Blood lactate dehydrogenase increased*†	21	3.53 (2.3, 5.42)	3.53 (2.29, 5.43)	38.03	1.82 (1.21)	3.53 (2.46)
	Blood calcium decreased*	18	3.51 (2.21, 5.58)	3.51 (2.19, 5.62)	32.23	1.81 (1.16)	3.5 (2.38)
	Gamma-glutamyltransferase increased*	27	3.24 (2.22, 4.73)	3.24 (2.23, 4.7)	41.78	1.69 (1.16)	3.24 (2.36)
	Blood creatine phosphokinase increased*	34	3.19 (2.28, 4.47)	3.19 (2.29, 4.45)	51.07	1.67 (1.19)	3.19 (2.4)
	Neutrophil count decreased	54	2.91 (2.23, 3.81)	2.91 (2.21, 3.83)	67.6	1.54 (1.16)	2.91 (2.32)
Nervous system disorders	Visual perseveration*	3	39.25 (12.48, 123.51)	39.25 (12.59, 122.33)	109.01	5.26 (3.82)	38.29 (14.67)
	Vasogenic cerebral oedema*	6	18.22 (8.14, 40.75)	18.21 (8.15, 40.67)	96.45	4.17 (3.09)	18.01 (9.18)
	Normal pressure hydrocephalus*	3	17.31 (5.55, 54.03)	17.31 (5.55, 53.95)	45.59	4.1 (2.67)	17.13 (6.61)
	Coma hepatic*	3	10.47 (3.36, 32.59)	10.47 (3.36, 32.63)	25.51	3.38 (1.96)	10.4 (4.02)
	Vocal cord paralysis*	5	6.28 (2.61, 15.12)	6.28 (2.6, 15.17)	22.11	2.65 (1.49)	6.26 (3)
	Cerebral thrombosis*	7	5.63 (2.68, 11.82)	5.62 (2.67, 11.84)	26.52	2.49 (1.49)	5.61 (3.01)
	Dysgeusia	185	5.49 (4.75, 6.34)	5.46 (4.76, 6.26)	671.61	2.44 (2.24)	5.44 (4.82)
	Brain oedema*†	19	3.59 (2.29, 5.63)	3.59 (2.29, 5.63)	35.37	1.84 (1.21)	3.58 (2.46)
	Ageusia*	35	3.37 (2.42, 4.69)	3.36 (2.41, 4.69)	58.03	1.75 (1.28)	3.36 (2.54)

Table 4 (continued)

SOC	PTs	Case reports	ROR (95%CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
General disorders and administration site conditions	Disease progression†	1092	21.07 (19.83, 22.4)	20.27 (19.11, 21.5)	19779.51	4.32 (4.24)	20.01 (19.02)
	Critical illness	3	8.84 (2.84, 27.51)	8.84 (2.84, 27.55)	20.74	3.14 (1.72)	8.8 (3.4)
	Oedema peripheral	346	7.34 (6.6, 8.16)	7.25 (6.57, 8)	1860.31	2.85 (2.7)	7.23 (6.61)
	Oedema	152	6.46 (5.5, 7.58)	6.43 (5.5, 7.52)	694.09	2.68 (2.45)	6.4 (5.6)
	Generalised oedema	31	6.26 (4.4, 8.92)	6.26 (4.4, 8.91)	136.42	2.64 (2.14)	6.24 (4.64)
	Performance status decreased	11	5.59 (3.09, 10.11)	5.59 (3.1, 10.06)	41.32	2.48 (1.66)	5.57 (3.4)
	Early satiety*	3	5.47 (1.76, 17.01)	5.47 (1.76, 17.05)	10.93	2.45 (1.03)	5.46 (2.11)
	Death†	2082	5.26 (5.03, 5.5)	4.93 (4.74, 5.13)	6614.05	2.3 (2.23)	4.92 (4.74)
	peripheral swelling*	253	3.09 (2.73, 3.5)	3.07 (2.73, 3.45)	353.47	1.62 (1.44)	3.07 (2.76)
Renal and urinary disorders	Renal hydrocele*	4	137.99 (49.58, 384.08)	137.97 (49.79, 382.31)	498.59	6.98 (5.66)	126.56 (53.74)
	Renal cyst haemorrhage*	3	24.35 (7.78, 76.19)	24.35 (7.81, 75.89)	66.11	4.58 (3.16)	23.98 (9.23)
	Renal haematoma*	3	11.95 (3.84, 37.22)	11.95 (3.83, 37.25)	29.87	3.57 (2.15)	11.86 (4.59)
	Renal cyst	43	11.67 (8.64, 15.76)	11.65 (8.68, 15.63)	415.67	3.53 (3.1)	11.57 (9)
	Renal vein thrombosis*	3	11.05 (3.55, 34.41)	11.05 (3.55, 34.44)	27.23	3.46 (2.04)	10.98 (4.24)
	RENAL impairment	144	3.72 (3.15, 4.38)	3.7 (3.16, 4.33)	283.69	1.89 (1.65)	3.7 (3.22)
Injury, poisoning and procedural complications	Recall phenomenon*	3	8.45 (2.72, 26.28)	8.45 (2.71, 26.34)	19.59	3.07 (1.65)	8.41 (3.25)
	Radiation injury*	3	7.78 (2.5, 24.21)	7.78 (2.5, 24.25)	17.64	2.95 (1.54)	7.75 (3)
	Radiation pneumonitis*	8	7.57 (3.78, 15.16)	7.56 (3.81, 15.01)	45.35	2.91 (1.97)	7.53 (4.21)
	Foreign body in respiratory tract*	4	4.78 (1.79, 12.75)	4.78 (1.79, 12.74)	11.91	2.25 (0.99)	4.76 (2.1)
	Foreign body*	8	3.59 (1.79, 7.18)	3.59 (1.81, 7.13)	14.89	1.84 (0.9)	3.58 (2)
Metabolism and nutrition disorders	Hypoproteinaemia	11	17.11 (9.44, 31.01)	17.11 (9.5, 30.8)	164.94	4.08 (3.26)	16.93 (10.29)
	Hypoalbuminaemia	35	11.1 (7.96, 15.48)	11.08 (7.94, 15.46)	318.76	3.46 (2.99)	11.01 (8.33)
	Feeding disorder	31	3.36 (2.36, 4.78)	3.35 (2.35, 4.77)	51.11	1.74 (1.24)	3.35 (2.49)
	Decreased appetite	299	2.73 (2.43, 3.06)	2.71 (2.41, 3.05)	322.62	1.44 (1.27)	2.7 (2.46)
Musculoskeletal and connective tissue disorders	Osteosclerosis*	4	5.11 (1.91, 13.64)	5.11 (1.92, 13.62)	13.18	2.35 (1.08)	5.1 (2.24)
Congenital, familial and genetic disorders	Gene mutation*	5	5.04 (2.09, 12.12)	5.04 (2.09, 12.18)	16.12	2.33 (1.17)	5.02 (2.41)
Blood and lymphatic system disorders	Myelosuppression	28	2.94 (2.03, 4.26)	2.94 (2.03, 4.27)	35.81	1.55 (1.03)	2.94 (2.15)

Note *New emerging findings of crizotinib-associated AEs from FAERS database; †Events may related to disease progression rather than adverse events associated with crizotinib

Abbreviations PTs Preferred Terms, *ROR* reporting odds ratio, *CI* confidence interval, *PRR* proportional reporting ratio, *χ2* chi-squared, *IC* information component, *EBGM* empirical Bayesian geometric mean

evaluations when necessary. It has been reported that crizotinib directly affects retinal function in rats [21], especially a decrease in the dark adaptation, which also needs further exploration of the mechanism of toxicity to provide rational use of crizotinib.

In previous clinical studies, the most common gastrointestinal disorders associated with crizotinib included nausea (51-59.1%), vomiting (39-50.9%), diarrhoea (47-65.5%), and constipation (28-45.6%), and such side-effects were usually mild or moderate (grade 1/2), with grade 3/4 side-effects in only 1-3% [8–11, 20]. These side effects also showed strong signals in this study, as shown in the "gastrointestinal disorders" subsection of Table 4. Usually, these toxic reactions do not require interruption or reduction of crizotinib administration and can be improved by supportive treatment. In the results of this analysis, in addition to the typical gastrointestinal toxicities, the relatively rare oesophagitis and oesophageal ulcers, as well as the resultant oesophageal spasm and dysphagia, are showing a modest number of cases. However, all four algorithms of these AEs have shown strong signals. It has been demonstrated that the ALK gene is involved in the development of the gastrointestinal tract, which could explain the more prevalent occurrence of gastrointestinal disorders using crizotinib [22]. It should be noted that gastrointestinal amyloidosis and reflux gastritis, which have not been previously reported, also showed strong signals, reminding us that

the gastrointestinal toxicity caused by crizotinib may go beyond that which has been reported in previous clinical studies. We need to continue to monitor the toxicity of such gastrointestinal reactions and update the instructions.

Anti-tumour agents, including chemotherapeutic agents, small molecule targeted agents, immune detection point inhibitors, and monoclonal antibodies, may cause cardiotoxicity. Cardiotoxicity is a common toxicity of ALK inhibitors and exists not only with crizotinib but also with second- and third-generation ALK inhibitors such as alectinib, ceritinib, and loratinib [22]. As illustrated in the "Cardiovascular Disorders" subsection of Table 4, our study not only found cardiotoxic signals such as bradycardia, QT interval prolongation, and cardiac failure, previously reported with crizotinib [8–11, 20], but also tapped into cardiac fibrillation and pericardial effusion, which had not been reported. In addition, we have found that the myocardial necrosis marker increased and blood creatine phosphokinase increased showing a strong signal, which indicates that crizotinib has a risk of myocardial infarction. The mechanism of cardiotoxicity caused by ALK-TKI is still unclear and should be further explored. Risk factors for cardiotoxicity associated with anti-tumour agents include age, heart disease, and concomitant use of beta-blockers. Therefore, clinicians should conduct dynamic monitoring, including electrocardiograms, cardiac enzymes, and cardiac ultrasound in high-risk groups, which may enhance the therapeutic benefit of taking crizotinib.

Pharmacological liver injury is a substantial adverse effect of TKIs. Hepatotoxicity of crizotinib in previous clinical studies was mainly manifested by elevated aminotransferases (30-39.2% in grades 1–4, 8-16% in grades 3–4) [9–11]. In our study, the results in the "hepatobiliary disorders" subsection of Table 4 showed hepatotoxicity included transaminases increased, alanine aminotransferase increased, liver function test increased, hepatitis, hepatotoxicity, and hepatocellular injury all showed strong signals, indicating a high incidence of hepatotoxicity. We also found strong signals for hepatitis fulminant and coma hepatic. Therefore, liver enzymes and bilirubin should be monitored regularly before and after crizotinib administration, and patients should be informed of the signs and symptoms of drug-induced hepatotoxicity and hepatic failure. Although cases of hepatitis fulminant and coma hepatic have been reported infrequently, it has undeniably emerged as a class of AEs that require adequate attention, and hepatotoxicity is usually ameliorated by dose reductions or temporary discontinuation of drugs with concomitant take of hepatoprotective medications.

Respiratory adverse reactions caused by crizotinib in previous clinical trials include pneumonia, emphysema, interstitial lung disease, dyspnoea, and respiratory failure. This study also identified new respiratory AEs such as pleural thickening, hydrothorax, pleural effusion, pleurisy, and haemoptysis, as depicted in the "Respiratory, Thoracic, and Mediating Disorders" subsection within Table 4. Although the prevalence of interstitial lung disease in the profile1005 study was only about 2% [9], the number of lung inflammation and interstitial lung disease cases was high, and the signal was strong in our analysis. A study that included 2028 patients found the incidence of interstitial lung disease associated with crizotinib treatment was 5.77%, with 3.45% displaying grade 3 or higher, and statistical analysis showed that age ≥ 55 years, ECOG scores of 2–4, a history of smoking, pre-existing or consolidated interstitial lung disease, and consolidated pleural effusion were significant risk factors for crizotinib-induced interstitial lung disease [23]. In contrast, another retrospective study found that two types of interstitial lung disease could be observed in patients treated with crizotinib. A severe, usually fatal ILD occurs within the first month of treatment, and a less severe ILD occurs later, with few clinical symptoms and predominantly presenting as a milled-glass shadow on CT scans. The prevalence of drug-related interstitial lung disease with crizotinib was 20.7%, a much higher frequency than in the clinical study (2.4%) [24]. Thus, in the real world, patients taking crizotinib may have a higher prevalence of interstitial lung disease because of non-severe respiratory symptoms and, therefore, missed without CT clarification. Two patients in profile1007 died from crizotinib-induced interstitial lung disease or pneumonia [10], and severe drug-related interstitial lung disease caused by crizotinib has been reported in the past, with patients presenting with rapidly progressive dyspnoea with severe hypoxaemia and diffuse interstitial infiltrates nine days after the start of crizotinib administration [25]. The pathogenesis of crizotinib-induced interstitial lung disease is not fully understood. However, experiments in vivo have been performed, and it was found that crizotinib blocks autophagic flow, leading to apoptosis of alveolar epithelial cells and promoting the recruitment of immune cells. In contrast, metformin can improve crizotinib-induced impaired lung function by restoring autophagic fluxes to reduce macrophage recruitment and pulmonary fibrosis [26], which provides a promising therapeutic strategy for treating crizotinib-induced pulmonary toxicity.

Venous thromboembolism (VTE) is a common complication in cancer treatment, and multiple studies have shown that lung cancer patients are more prone to VTE [27]. The proportion of VTE events in newly diagnosed lung cancer patients is as high as 13.2% [28]. In addition, the analysis of a phase II, prospective, multicenter, two-arm trial (METROS) found that the incidence of VTE

in advanced non-small cell lung cancer patients with ROS1 rearrangement was 3 to 5 times higher than that in general NSCLC patients [29]. A retrospective cohort study found that the proportion of pulmonary embolism in ALK-positive advanced non-small cell lung cancer patients who received crizotinib was 6.4% [30]. According to our research, crizotinib can also cause venous thrombosis limb, subclavian vein thrombosis, deep vein thrombosis, and pulmonary embolism. All of these AEs have shown strong signals in the "vascular disorders" subsection within Table 4. However, such VTE AEs have not been reported in previous clinical studies. Because of the high mortality rate of patients with VTE, it is necessary to conduct further studies to verify whether crizotinib can lead to an increased incidence rate of VTE, which will contribute to early diagnosis and better survival prognosis for patients.

Unexpectedly, it can be observed from the "infections and infections" subsection of Table 4 that crizotinib may lead to increased incidences of infections and infectious diseases, including perinephric abscess, oesophageal candidiasis, fungal oesophagitis, liver abscess, pneumocystis jirovecii pneumonia, and erysipelas, which have not been reported in previously registered clinical studies. The immune function of patients with malignant tumors may be suppressed, and they may exhibit impairments of T cell function under the influence of various inhibitory signals present in the tumor microenvironment [31]. In addition, patients who have received radiotherapy or chemotherapy in the past may suffer from myelosuppression, which may lead to the reduction of T cells and increase the rate of infectious diseases. Therefore, further studies are needed to confirm the potential.

However, there are limitations to this study. The FAERS database aggregates reports from diverse sources, including healthcare professionals, patients, and pharmaceutical companies. Some reports originate from non-professionals who may lack medical expertise, leading to inaccurate or incomplete descriptions of adverse reactions. These individuals might misattribute non-drug-induced symptoms as drug-related adverse events. Moreover, FAERS reports often lack rigorous scientific research and medical evidence, making the causal relationship between adverse events and drugs unclear. Reports typically indicate statistical associations rather than definitive causal links. As a voluntary reporting system, FAERS depends on the reporter's initiative, which may lead to a bias towards reporting severe adverse events while neglecting minor ones, potentially causing data overestimation or underestimation. Therefore, when utilizing FAERS data, it is crucial to conduct a comprehensive evaluation and validation in conjunction with other studies and clinical practices.

Conclusion

In the present study, we revealed the safety signal spectrum of crizotinib scientifically and systematically via analyzing pharmacovigilance analysis of the FAERS database. Common AEs, including visual impairment, gastrointestinal toxicity, hepatotoxicity, and cardiotoxicity, are frequent and essential. Regular monitoring and risk identification of all these AEs should be made in all populations. Unexpected and new significant AEs such as fulminant hepatitis, hepatic coma, deep vein thrombosis, pulmonary embolism, interstitial lung disease, pneumocystis jiroveci pneumonia, and myocardial infarction might also occur. Further studies are needed to verify these new AEs and further comprehend crizotinib's safety.

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Author contributions
The study design was developed by YW, JS and BL, while data collection and analysis were carried out by HZ and FX. The initial draft of the manuscript was prepared by HZ and FX, and subsequent revisions were made by YS, YL, LZ, JY, and HT as deemed necessary. All authors read and approved the final manuscript.

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Data availability
The article incorporates a substantial portion of the original data from this study, and for any additional information, inquiries can be directed to the corresponding authors.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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