

ORIGINAL RESEARCH ARTICLE

Real-world risk assessment of drug-induced cytokine release syndrome: Analysis of the Food and Drug Administration Adverse Event Reporting System

Qiong Guo¹, Weipeng Li, Huafeng Li, Niuniu Bai, Yayu Huo, and Hongxia Zhao*

Department of Pharmaceutical, Shanxi Bethune Hospital, Shanxi Academy of Medical Sciences, Tongji Shanxi Hospital, Third Hospital of Shanxi Medical University, Taiyuan, Shanxi, China

Abstract

Cytokine release syndrome (CRS) is a potentially life-threatening systemic inflammatory reaction associated with immunotherapies and other medications, yet its risk profile across marketed drugs remains poorly characterized. This study aims to evaluate the risk of drug-induced CRS using real-world data, thereby providing valuable insights for clinical medication safety assessment. We employed reporting odds ratios to assess the disproportionality in reports of drug-induced CRS from January 2004 to December 2024. Using univariate, least absolute shrinkage and selection operator, and multivariate regression analyses, we explored drugs associated with CRS, and the area under the curve was used to evaluate model performance. We collected a total of 13,499 reports. According to the Anatomical Therapeutic Chemical classification system, antineoplastic and immunomodulating agents were associated with the highest number of drug-related CRS cases ($n = 12,759$). Drug signal detection revealed that axicabtagene ciloleucel was linked to most CRS events ($n = 3,389$). Furthermore, among the top 50 drugs implicated in CRS, the prescribing information for 38 of them did not mention any association with CRS. Our findings demonstrate that antineoplastic and immunomodulating agents are the main drugs associated with CRS. A total of 18 drugs were identified as independent risk factors for drug-induced CRS. Alarming, most high-risk drugs lack relevant CRS warnings in their package leaflets. Clinicians should strengthen clinical monitoring for these medications, especially within one month after administration. Updated safety labeling and further relevant research are also required to ensure the safety of clinical medications.

Keywords: Cytokine release syndrome; Immunotherapy; Chimeric antigen receptor T-cell; Adverse events; Food and Drug Administration Adverse Event Reporting System

*Corresponding author:

Hongxia Zhao
(zhaohongxia@sxbqeh.com.cn)

Citation: Guo Q, Li W, Li H, Bai N, Huo Y, Zhao H. Real-world risk assessment of drug-induced cytokine release syndrome: Analysis of the Food and Drug Administration Adverse Event Reporting System. *Cancer Plus*. doi: 10.36922/CP025480081

Received: November 24, 2025**Revised:** June 25, 2026**Accepted:** July 10, 2026**Published online:** July 22, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

In recent years, with the continuous increase in the global incidence and mortality of cancer, traditional cancer treatment methods, such as surgery, radiotherapy, and chemotherapy, have difficulty achieving satisfactory clinical efficacy.¹⁻³ In the mid-1990s,

immunologists pioneered novel tumor immunotherapies that yielded prominent clinical efficacy.^{4,5} These therapies, including chimeric antigen receptor T-cell (CAR-T) therapy, immune checkpoint inhibitors, bispecific antibodies, and monoclonal antibodies, have revolutionized the landscape of cancer treatment by harnessing the body's own immune system to recognize and eliminate tumor cells with greater specificity. Nevertheless, immune-related adverse events (AEs) occur in certain patients, with cytokine release syndrome (CRS) being the most prevalent one.^{6,7}

Cytokine release syndrome is a severe systemic inflammatory response syndrome induced by the release of large amounts of cytokines when immune cells are activated.^{8,9} These cytokines include interleukin-6, tumor necrosis factor alpha, interferon gamma, and other pro-inflammatory mediators. The excessive and uncontrolled release of these cytokines triggers a cascade of inflammatory reactions, leading to widespread endothelial damage, vascular leakage, and multi-organ dysfunction. High fever, low blood pressure, hypoxia, and respiratory distress are typical symptoms of CRS.^{10,11} The incidence of CRS is not very high, yet it is often overlooked because of its rapid onset and difficulty in diagnosing, and can be life-threatening when treated inadequately.¹² Multiple factors can trigger CRS, including infections, immunotherapies, and drugs.^{13,14} At present, there are no comprehensive reports of drugs causing CRS. Most existing studies have focused on CRS caused by a class of immunotherapeutic agents and have lacked a comprehensive assessment of CRS risks across all marketed drugs. Accordingly, an integrated analysis of CRS using real-world data is required to uncover safety hazards, particularly adverse reactions absent from prescribing information.

As the world's largest spontaneous AE repository, the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) features a large sample size and standardized data, and has gained widespread recognition.¹⁵ It is applicable to AE analysis. Combined with data mining techniques, FAERS is also widely used for post-marketing drug safety surveillance and reassessment.¹⁶ This pharmacovigilance study aimed to systematically explore potential risk signals of drug-induced CRS. By extracting and assessing relevant signals from FAERS, we intend to promote rational and safe medication use for CRS. All patient data in this database are anonymized, and the study was exempted from ethical review per institutional requirements.

Post-marketing monitoring is one way to identify the correlation between drugs and adverse reactions.¹⁷ FAERS is a spontaneous reporting platform dedicated to gathering post-market AEs of drugs and biological therapies.¹⁸ Its

large dataset and open access make it a popular tool for mining drug safety signals.¹⁹ Prior works have adopted this database to explore links between certain medications (such as immune checkpoint inhibitors) and CRS.⁸ However, the association of drugs with CRS remains elusive. As novel targeted agents, immunotherapies, and combination treatments continue to emerge, the range of drugs that can trigger CRS is steadily growing. Current safety signals are inadequate to support clinical decision-making. Given the increasing number of newly approved drugs, updated CRS risk profiling is urgently needed. Notably, no prior research has yet systematically analyzed the overall correlation between various drugs and CRS risk.

This study aimed to systematically explore potential risk signals for drug-induced CRS using real-world data from the FAERS database. We intended to identify high-risk drugs associated with CRS, especially those without relevant warnings in package leaflets. The ultimate goal was to provide evidence for clinical safety monitoring, rational medication use, and post-marketing drug risk management.

2. Materials and methods

2.1. Data sources

This retrospective pharmacovigilance study relied on the FAERS database. Established for post-marketing monitoring of drugs and biological products, FAERS gathers AE reports and medication error records submitted to the FDA.²⁰ Data are voluntarily provided by medical staff and the general public, covering demographics, drug details, clinical outcomes, and other key information.²¹

We used the OpenVigil 2.1 pharmacovigilance analysis platform (<https://openvigil.sourceforge.net/>) to query the FAERS database, which has been publicly available since the first quarter of 2004 and is updated quarterly.²² This study downloaded the original ASCII package (Q12004–Q42024) and imported it into SAS 9.4 for data cleaning and statistical analysis.

2.2. Data mining

Since the database collects data through spontaneous reporting, some duplicate reports or reports have been withdrawn/deleted; the FDA official guidance document provides rules for corresponding data removal and a list of reports to be deleted.²³ This study performed data cleaning in strict accordance with the FDA's official guidance document on the website. The rule for data cleaning is to first remove duplicate reports using the recommended method by the FDA, select the PRIMARYID, CASEID, and FDA_DT fields of the DEMO table, sort according to CASEID, FDA_DT, and PRIMARYID, keep the report

with the largest FDA_DT value, and the largest reserved PRIMARYID value for both CASEID and FDA_DT. Secondly, since the first quarter of 2019, there has been a deleted report list in each quarter's data package. After the data was removed, the report was removed according to the CASEID in the deleted report list.

2.3. Data standardization

Adverse event names in the FAERS database were coded using the Medical Dictionary for Regulatory Activities (MedDRA) 27.1, and drug names were standardized using the World Health Organization's Drug Dictionary.

Since the names of AEs in the FAERS database are described using preferred terms in the MedDRA, and given that the MedDRA Dictionary is updated annually in March and September, each update involves adjustments in the preferred terms hierarchy and changes in the corresponding system organ class. Therefore, this study used the latest version of MedDRA dictionary to recalibrate the preferred terms in FAERS database, and obtained the system organ class and preferred terms in the latest version of MedDRA dictionary for subsequent analysis.²⁴

2.4. Data filtering

In this study, a total of 22,375,298 patient-reported data points were obtained from the FAERS database, and 3,761,306 duplicate cases reported by the same patients were removed in accordance with the FDA's deduplication reporting rules. A total of 18,613,992 patient cases remained after deduplication, involving 18,963,792 AEs and 55,357,463 AE reports (one patient could report multiple AEs at the same time; therefore, a single report may contain multiple AEs). Target AEs were screened using preferred terms in the MedDRA dictionary (related terms are shown in Table 1), and a total of 13,476 patients with target AEs were identified, involving 13,499 target AE reports.

Table 1. List of target adverse event filtering terms

Preferred language coding	Preferred language
10050685	Cytokine storm
10052015	Cytokine release syndrome

2.5. Data analysis methods

We used the reporting odds ratio (ROR)²⁵ of the disproportional method to detect drug-induced CRS signaling. The RORs were calculated by using a two-by-two contingency table, as shown in Table 2.

Table 2. Two-by-two contingency table for disproportionality analysis

Variables	Cytokine release syndrome	Other adverse events	Total
Target drugs	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	a + b + c + d

Disproportionality analysis was applied to explore potential links between medications and CRS. This approach compares observed and expected counts of drug-AEs; a result beyond the predefined threshold signals an imbalanced distribution.²⁶ ROR and proportional reporting ratio (PRR) are the two mainstream frequency-based metrics for such analysis, featuring straightforward computation and stable outcomes.^{27,28} The calculation equation and criteria are listed in Table 3. A relatively higher ROR or PRR indicates a stronger statistical relationship between the suspect drug and suspect AEs.

We performed a univariate analysis on suspected drugs, screening for those with a lower bound of the 95% confidence interval (CI) showing ROR > 1, a > 100, and *p*-adjust < 0.01. *p*-adjust refers to the *p*-value obtained after applying Fisher's exact test and the Bonferroni correction. In the univariate analysis, drugs with *p* < 0.01 were selected for the least absolute shrinkage and selection operator (LASSO) model. Individuals with missing data (such as gender or age) were excluded from this study. By optimizing the penalty parameter (λ) through 10-fold cross-validation, LASSO identified a streamlined subset of variables. Subsequently, a multivariate logistic regression analysis was conducted, incorporating age and gender to identify risk factors for drug-induced CRS.²⁹ The model's performance was evaluated using area under the curve (AUC).

Data processing and analysis were predominantly performed using Microsoft Excel 2019, GraphPad Prism 9, and R software (version 4.2.1).

3. Results

3.1. Descriptive analysis

In this study, a total of 22,375,298 patient-reported data were obtained from the FAERS database, and 3,761,306 cases of repeated data reported by the same patients were removed in accordance with the FDA's weight-removal reporting rules. After weight removal, 18,613,992 patients remained. There were 18,963,792 AEs and 55,357,463 AE

Table 3. The principles of disproportionate measurement and the criteria for signal detection

Method	Calculation formula	Criteria
ROR	$ROR = \frac{a/c}{b/d}$	
	$SE(\ln ROR) = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$	$a \geq 3$; 95% CI (lower limit) > 1
	$95\%CI = e^{\ln(ROR) \pm 1.96se}$	
PRR	$PRR = \frac{a/(a+b)}{c/(c+d)}$	
	$SE(\ln PRR) = \sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}$	$a \geq 3$; 95% CI (lower limit) > 1
	$95\%CI = e^{\ln(ROR) \pm 1.96se}$	
	$\chi^2 = \frac{(ad - bc)^2 (a + b + c + d)}{(a + b)(a + c)(c + d)(b + d)}$	$a \geq 3$; $PRR \geq 2$; $\chi^2 \geq 4$
	$E(IC) = \log_2 \frac{(a + \gamma 1)(a + b + c + d + \alpha)(a + b + c + d + \beta)}{(a + b + c + d + \gamma)(a + b + \alpha 1)(a + c + \beta 1)}$	-

Abbreviations: CI: Confidence interval; PRR: Proportional reporting ratio; ROR: Reporting odds ratio.

reports. Target AEs were screened using preferred terms in the MedDRA dictionary, yielding 13,476 patients with target AEs and 13,499 target AE reports. The data mining and processing procedure for cases with drug-related CRS is shown in Figure 1.

Figure 2 intuitively depicts the yearly variation in non-fatal, fatal, and overall CRS case counts from 2004 to 2024. The number of CRS reports remained low before 2018, then rose sharply over the years, reaching its highest level in 2024. The proportion of fatal cases also increased gradually over the study period. The sharp increase in CRS reports after 2018 is highly consistent with the large-scale clinical application of novel immunotherapies, such as CAR-T and bispecific antibodies, directly reflecting the close correlation between the use of new drugs and the occurrence of CRS.

Table 4 details the clinical characteristics across all 13,476 reports. CRS cases were most common in patients aged >65 years (32.21%), with successive declines in the 45–64 (27.02%), 18–44 (11.21%), and ≤18 years (5.13%) groups. Advanced age is accompanied by immune senescence, prevalent comorbidities, and diminished organ adaptability, increasing the risk of severe inflammatory

reactions elicited by medications. Furthermore, males exhibited a higher incidence of CRS (48.43%) than females (32.82%). The male predominance may be related to the higher incidence of malignant tumors in men and differences in immune response and drug metabolism between genders. Among these reports, the most frequently reported outcomes were initial or prolonged hospitalization (48.92%), followed by death (18.01%), life-threatening events (11.14%), disability (1.28%), interventions required to prevent permanent impairment (0.46%), and congenital anomaly (0.02%). The extremely high proportion of serious adverse outcomes highlights the severe clinical harm of drug-induced CRS and the urgency of strengthening risk prevention and control. The six most frequently reported clinical outcomes were all serious AEs, with substantial impacts on patient health and quality of life. These outcomes underscore the severity of drug-induced CRS and highlight the need for greater clinical awareness and vigilance. In addition, aside from 691 cases reported by consumers and 743 cases reported by those who did not specify, the remaining cases were reported by healthcare professionals. The majority of reports from healthcare professionals help ensure the authenticity and accuracy of AE descriptions, reducing bias in self-reported

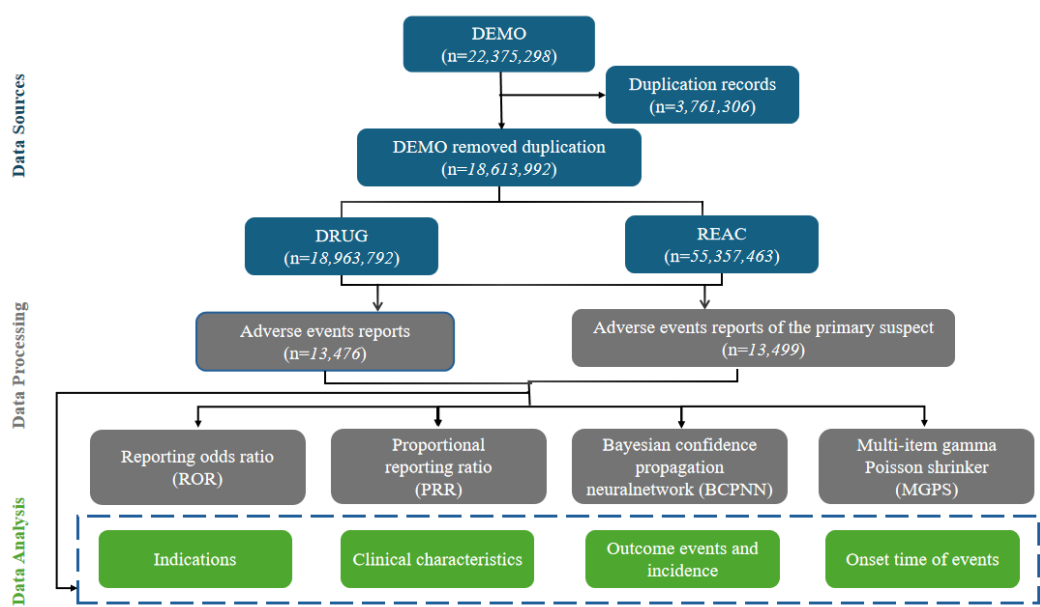


Figure 1. Flowchart of the data-mining process for drug-related cytokine release syndrome

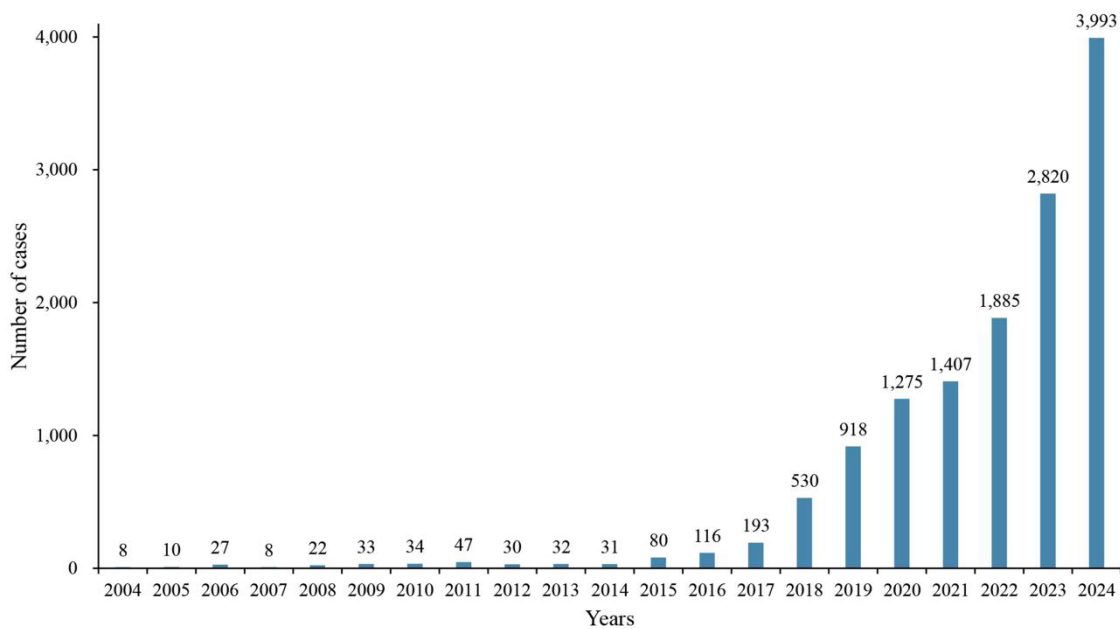


Figure 2. Number of reports of drug-associated cytokine release syndrome

Table 4. Clinical characteristics of drug-induced cytokine release syndrome reports from the Food and Drug Administration Adverse Event Reporting System

Variables	Non-fatal		Fatal		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Gender						
Female	3,670	33.22	753	31.03	4,423	32.82
Male	5,275	47.74	1,251	51.55	6,526	48.43
Not specified	2,104	19.04	423	17.43	2,527	18.75
Age (years)						
<18	538	4.87	153	6.30	691	5.13
18–44	1,226	11.10	284	11.70	1,510	11.21
45–64	3,026	27.39	615	25.34	3,641	27.02
≥65	3,546	32.09	795	32.76	4,341	32.21
Not specified	2,713	24.55	580	23.90	3,293	24.44
Reported year						
2004	8	0.07	–	–	8	0.06
2005	7	0.06	3	0.12	10	0.07
2006	21	0.19	6	0.25	27	0.20
2007	7	0.06	1	0.04	8	0.06
2008	18	0.16	4	0.16	22	0.16
2009	32	0.29	1	0.04	33	0.24
2010	29	0.26	5	0.21	34	0.25
2011	38	0.34	9	0.37	47	0.35
2012	20	0.18	10	0.41	30	0.22
2013	27	0.24	5	0.21	32	0.24
2014	22	0.20	8	0.33	30	0.22
2015	71	0.64	9	0.37	80	0.59
2016	88	0.80	28	1.15	116	0.86
2017	171	1.27	22	0.16	193	1.43
2018	460	4.16	70	2.88	530	3.93
2019	788	7.13	122	5.03	910	6.75
2020	1,008	9.12	264	10.88	1,272	9.44
2021	1,145	10.36	260	10.71	1,405	10.43
2022	1,502	13.59	379	15.62	1,881	13.96
2023	2,349	21.26	468	19.28	2,817	20.90
2024	3,238	29.31	753	31.03	3,991	29.62
Country						
United States of America	5,966	54.00	920	37.91	6,886	51.10
Japan	1,026	9.29	391	16.11	1,417	10.51
France	797	7.21	164	6.76	961	7.13
Spain	480	4.34	81	3.34	561	4.16
Germany	378	3.42	120	4.94	498	3.70

(Cont'd...)

Table 4. (Continued)

Variables	Non-fatal		Fatal		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Italy	258	2.34	107	4.41	365	2.71
Canada	316	2.86	47	1.94	363	2.69
China	278	2.52	67	2.76	345	2.56
United Kingdom	244	2.21	72	2.97	316	2.34
Other	1,240	11.22	439	18.09	1,679	12.46
Not specified	66	0.60	19	0.78	85	0.63
Reporter						
Physician	4,778	43.24	1,296	53.40	6,074	45.07
Pharmacist	4,227	38.26	844	34.78	5,071	37.63
Other health-professional	774	7.01	123	5.07	897	6.66
Consumer	593	5.37	98	4.04	691	5.13
Not specified	677	6.13	66	2.72	743	5.51

data from non-professionals. CRS AEs occurred during 0–30 days ($n = 5,937$, 44.06%), and the incidence gradually decreased after 31–60 days ($n = 221$, 1.64%). The onset times of AEs, stratified by age and gender, are presented in Figure 3. The mean time for adverse reactions was 17.9 days. The short onset time of 30 days suggests that clinical monitoring of CRS should be strengthened in the early post-administration period, especially within the first month, to enable early detection and intervention.

3.2. Disproportionality analysis

The 50 drugs most frequently reported for CRS-associated AEs are summarized in Figure 4. Axicabtagene ciloleuce (3,389 cases) is the most frequently reported drug, followed by tisagenlecleuce (1,228 cases), blinatumomab (704 cases), brexucabtagene autoleuce (654 cases), idcabtagene vicleuce (501 cases), fludarabine (470 cases), rituximab (456 cases), cyclophosphamide (377 cases), teclistamab (357 cases), and ciltacabtagene autoleuce (355 cases). These top-ranked drugs are mainly novel immunotherapies and cytotoxic chemotherapeutic agents, which are widely used in the treatment of hematological malignancies and solid tumors, and their high exposure rates are an important reason for the high number of CRS reports. Of these 50 drugs, 12 drugs indicated CRS risk in their package leaflet, while the remaining 38 drugs did not. The 38 drugs are fludarabine, rituximab, cyclophosphamide, brexucabtagene autoleuce, epcoritamab, oxaliplatin, ipilimumab, nivolumab, dexamethasone, lenalidomide, pembrolizumab, doxorubicin, atezolizumab, durvalumab, obinutuzumab, antithymocyte immunoglobulin,

carboplatin, tocilizumab, tebentafusp, gemcitabine, bendamustine, daratumumab, prednisone, mycophenolic acid, alemtuzumab, bortezomib, lenvatinib, carfilzomib, methotrexate, filgrastim, prednisolone, tacrolimus, ruxolitinib, vincristine, methylprednisolone, trastuzumab, and bevacizumab. This finding reveals a serious safety information gap: most drugs with significant CRS risk have not been labeled with relevant warnings, which greatly increases the risk of clinical use.

There were 339 “primary suspected drugs” involved in the reported target AEs, and 50 drugs met the signal detection criteria in this study, as detailed in Table 5. Idecabtagene vicleuce (ROR: 1,015.29; 95% CI: 919.63–1,120.89) reported the highest ROR for CRS, followed by tarlatamab (970.84; 95% CI: 794.57–1,186.23), axicabtagene ciloleuce (944.51; 95% CI: 906.26–984.38), brexucabtagene autoleuce (811.30; 95% CI: 744.95–883.56), lisocabtagene maraleuce (736.92; 95% CI: 636.38–853.34), glofitamab (563.37; 95% CI: 482.72–657.49), epcoritamab (543.78; 95% CI: 482.60–612.71), mosunetuzumab (498.40; 95% CI: 402.56–617.06), teclistamab (397.91; 95% CI: 356.51–444.12), elranatamab (394.41; 95% CI: 322.62–482.17), and ciltacabtagene autoleuce (393.43; 95% CI: 352.41–439.23). The extremely high ROR values of these drugs indicate a strong statistical association with CRS, and they are confirmed as high-risk drugs for inducing CRS.

Based on the PRR criteria, the top 50 drugs by PRR were consistent with the ROR results. The high consistency between ROR and PRR results further confirms the reliability of the detected CRS risk signals and rules out spurious signals.

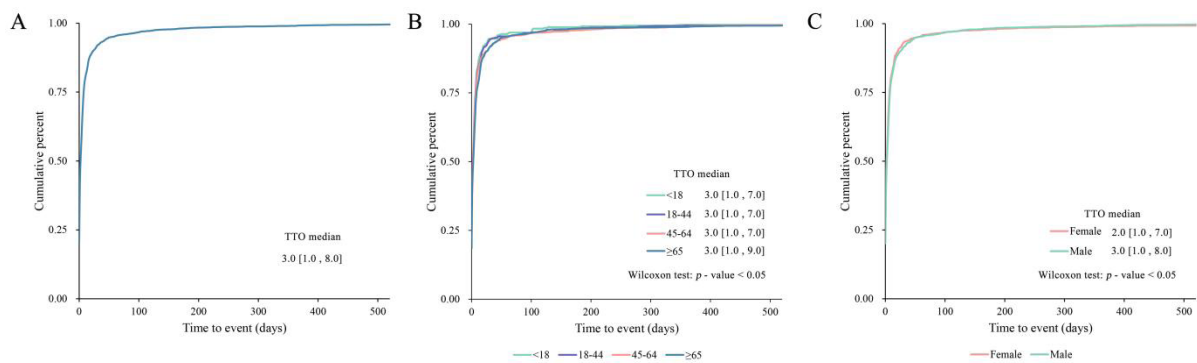


Figure 3. Statistics on the onset time of drug-related cytokine release syndrome. (A) Onset time of all drug-related cytokine release syndromes. (B) Onset-time statistics for drug-related cytokine release syndromes across age groups. (C) Onset-time statistics for drug-related cytokine release syndromes across genders.

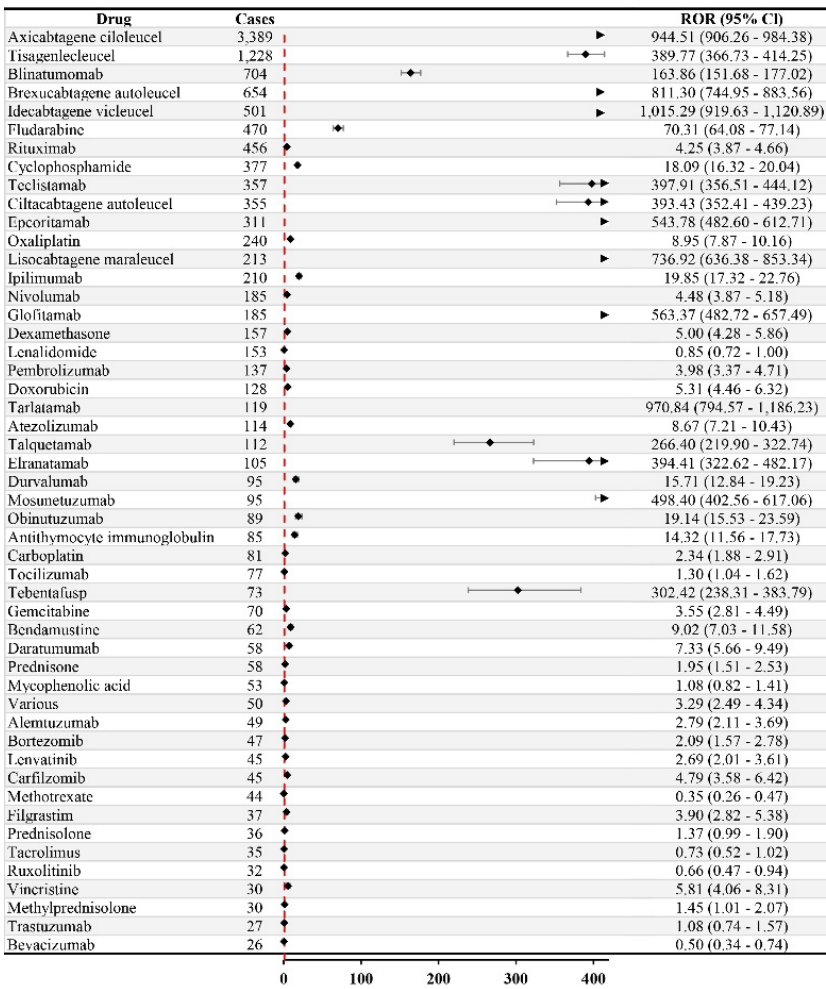


Figure 4. Signal strength of adverse events at the drug level ranked by reports
Abbreviations: CI: Confidence interval; PRR: Proportional reporting ratio; ROR: Reporting odds ratio.

3.3. Drugs associated with increased cytokine release syndrome risk

To assess the risk signals associated with medications that cause CRS, the analysis focused on the top 50 drugs with sufficient reporting data. The top 50 drugs causing CRS were classified into the following 10 categories: (i) antineoplastic and immunomodulating agents, (ii) sensory organs, (iii) dermatologicals, (iv) alimentary tract and metabolism, (v) systemic hormonal preparations (excluding sex hormones and insulin), (v) cardiovascular system, (vi) respiratory system, (vii) anti-infectives for systemic use, (ix) various, and (x) musculoskeletal system. Classifying drugs according to the Anatomical Therapeutic Chemical Classification System helps clarify the CRS risk characteristics of different therapeutic categories and provides targeted guidance for clinical medication across different disease systems (Table 5).

We conducted a single-factor analysis for drugs with >100 cases, a lower 95% CI limit of ROR > 1, and p -adjust < 0.01. All drugs yielding $p < 0.01$ in univariate analysis were first analyzed via LASSO regression. On this basis, multivariate logistic regression was conducted, with age and gender as covariates (Figure 5B and 5C). The results showed that 18 drugs were independent drug-induced CRS risk factors (Figure 5A). The identification of 18 drugs as independent risk factors provides a clear list of high-alert drugs for clinical practice, helping clinicians

prioritize monitoring when using them. The AUC, which represents the model's predictive accuracy, was 0.594 (Figure 6). The AUC indicates that the model has moderate predictive performance, providing a useful reference for risk assessment of drug-induced CRS. These drugs' indications were classified as antineoplastic and immunomodulating agents (15/18), systemic hormonal preparations (excluding sex hormones and insulin) (2/18), and various (1/18). The absolute dominance of antineoplastic and immunomodulating agents further confirms that this category is the core high-risk group for CRS, which is the focus of clinical pharmacovigilance.

4. Discussion

To our knowledge, this study is the first large-scale real-world analysis to leverage the FAERS pharmacovigilance system to evaluate AEs secondary to drug-induced CRS. We characterized the clinical manifestations of these reactions and identified drugs with the strongest associations with CRS. Although CRS is listed in the prescribing information for some of these drugs, many others do not include this warning despite evidence suggesting a potential risk. Consequently, the risk of cytokine release syndrome associated with these drugs may be underrecognized in clinical practice. This study reveals a major safety hazard in clinical medication: the lack of CRS risk warnings for most high-risk drugs may lead to delayed intervention and poor patient prognosis.

Table 5. Signal strength of adverse events at the ATC level in the Food and Drug Administration Adverse Event Reporting System

ATC name	ATC code	Case reports	ROR (95% CI)	PRR (95% CI)
Antineoplastic and immunomodulating agents	L	12,759	29.66 (27.54–31.94)	29.64 (27.53–31.92)
Sensory organs	S	449	0.47 (0.43–0.52)	0.47 (0.43–0.52)
Dermatologicals	D	436	0.27 (0.25–0.30)	0.27 (0.25–0.30)
Alimentary tract and metabolism	A	354	0.17 (0.16–0.19)	0.17 (0.16–0.19)
Systemic hormonal preparations (excluding sex hormones and insulin)	H	292	0.56 (0.50–0.63)	0.56 (0.50–0.63)
Cardiovascular system	C	260	0.19 (0.17–0.21)	0.19 (0.17–0.21)
Respiratory system	R	241	0.22 (0.20–0.25)	0.22 (0.20–0.25)
Anti-infectives for systemic use	J	138	0.16 (0.14–0.19)	0.16 (0.14–0.19)
Various	V	100	0.26 (0.21–0.31)	0.26 (0.21–0.31)
Musculoskeletal system	M	91	0.12 (0.10–0.14)	0.12 (0.10–0.14)
Nervous system	N	89	0.03 (0.02–0.04)	0.03 (0.02–0.04)
Genito-urinary system and sex hormones	G	71	0.06 (0.05–0.07)	0.06 (0.05–0.07)
Blood and blood-forming organs	B	25	0.03 (0.02–0.04)	0.03 (0.02–0.04)
Antiparasitic products, insecticides, and repellents	P	8	0.16 (0.08–0.32)	0.16 (0.08–0.32)

Abbreviations: ATC: Anatomical Therapeutic Chemical Classification System; CI: Confidence interval; PRR: Proportional reporting ratio; ROR: Reporting odds ratio.

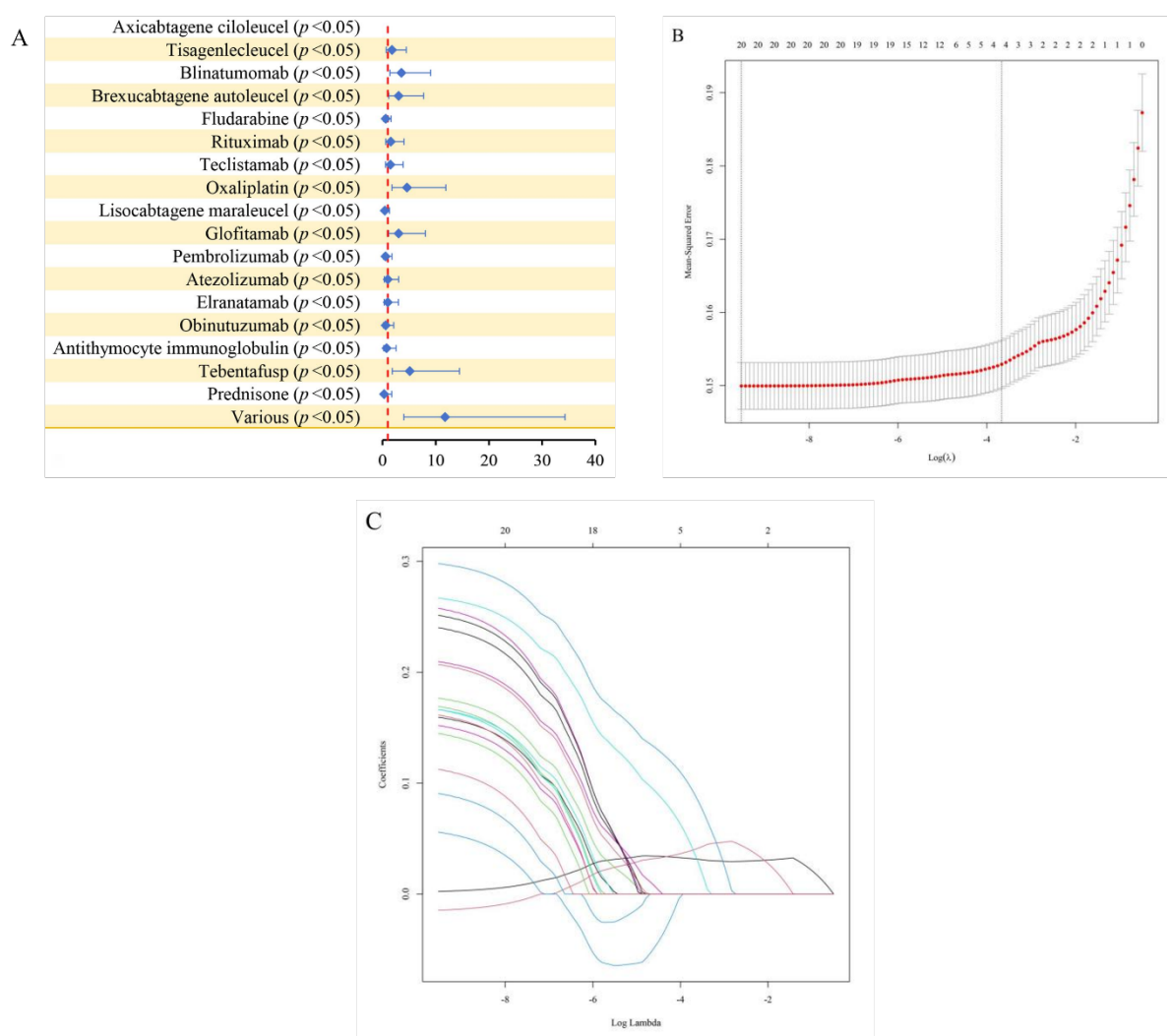


Figure 5. Single- and multi-factor analysis of drug-induced cytokine release syndrome (CRS). (A) Eighteen drugs that were independent drug-induced CRS risk factors. (B) The optimal regularization λ of LASSO regression. (C) The coefficient trajectories for each variable at different values of λ . Abbreviations: LASSO: Least absolute shrinkage and selection operator; ROR: Reporting odds ratio.

The top 50 drugs include various types, such as CAR-T, immune checkpoint inhibitors, bispecific antibodies, monoclonal antibodies, cytotoxic drugs, and hormones. Among these, almost all drugs in the CAR-T category (such as axicabtagene ciloleucel, tisagenlecleucel, brexucabtagene autoleucel, idcabtagene vicleucel, ciltacabtagene autoleucel, and lisocabtagene maraleucel) and bispecific antibody category (such as blinatumomab, teclistamab, nivolumab, tarlatamab, talquetamab, elranatamab, and mosunetuzumab) can cause CRS, with clear warnings in the package leaflet. The high CRS risk with CAR-T and bispecific antibodies is due to their mechanism of action,

which directly activates T cells to release large amounts of cytokines, triggering a strong inflammatory response. This is also in line with the conclusions of relevant reports.³⁰ However, the package leaflets for monoclonal antibodies, cytotoxic drugs, and hormones rarely mention CRS as a potential adverse reaction. This study found that the ROR values for fludarabine, cyclophosphamide, and oxaliplatin were higher, indicating a high risk of CRS with these drugs and the need for close monitoring during clinical use. Once patients with CRS were identified, supportive measures could be implemented to manage symptoms and prevent serious clinical outcomes.

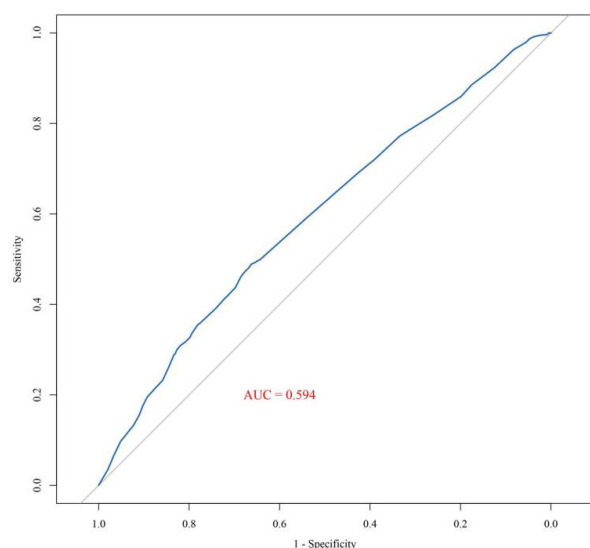


Figure 6. Area under the curve (AUC) of multifactorial logistic regression analysis

This study identified various demographic and clinical characteristics, including a predominance of male patients, patients aged over 65, and the use of antineoplastic and immunomodulating agents. This is consistent with the results of epidemiological studies in cancer epidemiology, in which men have a higher incidence of cancer than women,³¹ and most cases occur after age 60.³² The consistent demographic characteristics confirm that the CRS risk in this study is closely related to the distribution of cancer patients in the population, and the research results are highly representative of clinical practice.

Since the first monoclonal antibody was used in a pioneering application, the clinical use of immunotherapies has grown exponentially over the past decade.³³ Currently, global regulatory authorities have approved multiple antibody drugs that cover a wide range of diseases, from cancer to autoimmune disorders.³⁴ However, the clinical application of such drugs is also accompanied by corresponding adverse reactions, among which CRS is the most common.^{10,13} This phenomenon is highly consistent with the findings of this study: on the one hand, the incidence of CRS adverse reactions has shown an exponential upward trend since 2018; on the other hand, its clinical manifestations are widely distributed across tumor fields, sensory organs, dermatology, and other immune-related disease categories. The rapid growth of CRS reports parallels the rapid popularization of immunotherapies, reminding the medical community to pay equal attention to the efficacy and safety of new drugs as they are promoted.

Cytokine release syndrome is an immune cascade

triggered by direct lysis of target cells or by therapeutic activation of T cells. During this process, T cells produce cytokines such as interferon gamma and tumor necrosis factor alpha, which in turn activate innate immune cells such as macrophages and endothelial cells; these activated cells subsequently release large amounts of pro-inflammatory cytokines such as interleukin-6, and through a positive feedback loop, continuously trigger a cytokine storm, leading to systemic inflammatory responses, vascular leakage, hypotension, and multi-organ dysfunction.³⁵⁻³⁸ The uncontrolled release of inflammatory mediators can further activate the coagulation cascade and the complement system, exacerbating tissue damage. Persistent activation of immune cells results in a hyperinflammatory state that may progress to hemophagocytic lymphohistiocytosis-like manifestations, characterized by prolonged fever, cytopenias, hyperferritinemia, and hepatosplenic dysfunction.¹⁰ In severe cases, patients develop respiratory distress, acute kidney injury, cardiac dysfunction, or even fatal outcomes. Therefore, timely identification and intervention are critical. Therapeutic strategies include blockade of interleukin-6 signaling using tocilizumab, administration of corticosteroids, and supportive intensive care. Disrupting the positive feedback loop at an early stage helps restore immune homeostasis and prevent irreversible organ damage, while preserving the antitumor efficacy of T-cell-based immunotherapies.

Research reports indicate that CRS typically occurs 2 to 3 days after infusion, with initial symptoms that are mild and gradually progress over several hours to several days. Some patients develop symptoms within 14 days of receiving the infusion, which persist for 7 to 8 days. This is largely consistent with the result of this study, which found that the median onset time of CRS was three days.³⁹ The consistent onset time provides a clear window for clinical monitoring: clinicians should intensify monitoring within 1–2 weeks after drug administration, especially during the first three days.

The clinical manifestations of CRS are diverse, ranging from mild flu-like symptoms to life-threatening severe inflammatory responses, and often involve multiple organ systems. Among them, mild symptoms include fever, fatigue, headache, rash, joint pain, and muscle pain. For mild CRS, symptomatic treatment with appropriate drugs can alleviate symptoms, such as fever; ice baths, cooling blankets, and acetaminophen can be used, but non-steroidal anti-inflammatory drugs are prohibited.¹⁸ More severe CRS is characterized by low blood pressure and high fever, which may progress to an uncontrolled systemic inflammatory response, presenting symptoms such as shock requiring vasopressor maintenance of circulation,

vascular leakage, disseminated intravascular coagulation, and multiple organ system failure. For patients with severe CRS, treatment options include blocking the release of interleukin-6 (such as tocilizumab) and interleukin-1 (such as anakinra) by monocytes, blocking the release of tumor necrosis factor alpha by upstream T cells, or using Janus kinase inhibitors (these inhibitors can inhibit cytokine release without affecting the cytotoxicity of T cells). Additionally, some studies suggest implementing preventive cytokine blocking measures as early as possible to reduce cytokine release during the early treatment period while not affecting the cytotoxicity of T cells.¹³

5. Limitations

This study has several inherent limitations. The data were obtained from a spontaneous reporting database, a resource susceptible to reporting biases including underascertainment, duplicate reports, and stimulated reporting, which may distort analytical results. Moreover, the dataset is suboptimal in terms of quality and completeness.⁴⁰ Spontaneous reporting systems often exhibit underreporting of mild AEs and overreporting of serious AEs, which may affect the accuracy of risk frequency assessments. The quality and completeness of the data are also less than optimal. Nevertheless, the findings from this data-mining effort have meaningful implications for promoting safe and rational pharmacotherapy. It must be clarified that all detected safety signals merely suggest statistical associations, rather than verifying prevalence or causal relationships. Signal magnitude reflects only relative risk and cannot quantify absolute risk. Furthermore, age and gender were the sole covariates incorporated in the statistical model. Uncontrolled confounding variables may therefore compromise the validity of analyses. Of particular note, potential drug interactions, baseline comorbidities, and polypharmacy were not evaluated in this study, despite their established impacts on the development of drug-associated adverse conditions. The lack of comprehensive adjustment for confounding factors is a common limitation of FAERS database research, which should be addressed in future studies with more detailed clinical data.

6. Conclusion

In this study, we utilized the FAERS database to comprehensively assess drug-induced CRS and associated medications. Using disproportionality analysis and regression modeling, we evaluated real-world CRS risks and identified 18 drugs as independent risk factors. Antineoplastic and immunomodulating agents are the top drug category in our dataset, with the highest number of

CRS reports. Importantly, the vast majority of drugs within this high-risk group contain no CRS-related precautionary advice in their package inserts, creating a notable clinical safety deficiency. Given the life-threatening potential of CRS, clinicians must maintain strict vigilance and reinforce patient monitoring when prescribing these medications. Further epidemiological research is necessary to fully elucidate the association between these drugs and the onset of CRS.

Acknowledgments

None.

Funding

This work was funded by the research project of Shanxi Provincial Drug Regulatory Science Research Association (No. JYJY-2025-ZD-015).

Conflict of interest

The authors have no relevant affiliations or financial involvement with any organization or entity that has a financial interest in, or financial conflict with, the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Author contributions

Conceptualization: Qiong Guo, Weipeng Li

Formal analysis: Weipeng Li

Investigation: Yayu Huo, Niuniu Bai

Methodology: Weipeng Li, Huafeng Li

Writing—original draft: Qiong Guo

Writing—review & editing: Qiong Guo, Hongxia Zhao

Ethics approval and consent to participate

This study does not involve human subjects, animal experiments, or any research activities that require ethical review in accordance with the Declaration of Helsinki and local ethical guidelines. Therefore, no ethical approval was required for this study.

Consent for publication

Not applicable.

Availability of data

The data for this study were obtained from the FAERS database (<https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard>).

References

- Zhu L, Zhu J, Wang Q, *et al.* Global, regional, and national burden of 34 cancer groups across 204 countries and territories, 1990-2021, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Front Oncol.* 2025;15:1660125.
doi: 10.3389/fonc.2025.1660125
- Zafar A, Khatoon S, Khan MJ, Abu J, Naeem A. Advancements and limitations in traditional anti-cancer therapies: a comprehensive review of surgery, chemotherapy, radiation therapy, and hormonal therapy. *Discov Oncol.* 2025;16(1):607.
doi: 10.1007/s12672-025-02198-8
- Helmberger T. The evolution of interventional oncology in the 21st century. *Br J Radiol.* Sep 1 2020;93(1113):20200112.
doi: 10.1259/bjr.20200112
- Tan S, Li D, Zhu X. Cancer immunotherapy: Pros, cons and beyond. *Biomed Pharmacother.* 2020;124:109821.
doi: 10.1016/j.biopha.2020.109821
- Nakajima F, Khanna A, Xu G, *et al.* Immunotherapy with anti-CD3 monoclonal antibodies and recombinant interleukin 2: stimulation of molecular programs of cytotoxic killer cells and induction of tumor regression. *Proc Natl Acad Sci USA.* 1994;91(17):7889–7893.
doi: 10.1073/pnas.91.17.7889
- Wang J, Arora K, de Lima M. Cytokine release syndrome after allogeneic hematopoietic stem cell transplantation using posttransplant cyclophosphamide: current understanding and management. *Front Immunol.* 2026;17:1642583.
doi: 10.3389/fimmu.2026.1642583
- Arvanitis P, Tziotis A, Papadimitos S, Farmakiotis D. Pathogenesis, Diagnosis, and Management of Cytokine Release Syndrome in Patients with Cancer: Focus on Infectious Disease Considerations. *Curr Oncol.* 2025;32(4):198.
doi: 10.3390/curroncol32040198
- Xi X, Yan X, Chen Y, *et al.* Cytokine release syndrome associated with immune checkpoint inhibitors: a pharmacovigilance study based on spontaneous reports in FAERS. *Expert Opin Drug Saf.* 2025;24(7):839–846.
doi: 10.1080/14740338.2024.2385489
- Ozaki T, Yumita S, Ogasawara S, *et al.* Cytokine release syndrome following durvalumab and tremelimumab in advanced hepatocellular carcinoma: A case report with cytokine and damage-associated molecular pattern analysis. *Hepatol Res.* 2024;55(2):291–297.
doi: 10.1111/hepr.14088
- Lee DW, Gardner R, Porter DL, *et al.* Current concepts in the diagnosis and management of cytokine release syndrome. *Blood.* 2014;124(2):188–195.
doi: 10.1182/blood-2014-05-552729
- Santomasso BD, Nastoupil LJ, Adkins S, *et al.* Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline. *J Clin Oncol.* 2021;39(35):3978–3992.
doi: 10.1200/jco.21.01992
- Liu D, Zhao J. Cytokine release syndrome: grading, modeling, and new therapy. *J Hematol Oncol.* 2018;11(1):121.
doi: 10.1186/s13045-018-0653-x
- Radtke KK, Bender BC, Li Z, *et al.* Clinical Pharmacology of Cytokine Release Syndrome with T-Cell-Engaging Bispecific Antibodies: Current Insights and Drug Development Strategies. *Clin Cancer Res.* 2025;31(2):245–257.
doi: 10.1158/1078-0432.Ccr-24-2247
- Chen P, Tang Y, He W, *et al.* Potential Pathophysiological Mechanisms Underlying Multiple Organ Dysfunction in Cytokine Release Syndrome. *Mediators Inflamm.* 2022;2022:1-17.
doi: 10.1155/2022/7137900
- Salem JE, Manouchehri A, Moey M, *et al.* Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol.* 2018;19(12):1579–1589.
doi: 10.1016/s1470-2045(18)30608-9
- Liu H, Yang Q, Li Z, Yan S, Ming S. Systematic analysis of sugammadex-related adverse drug reaction signals using FAERS database. *Int J Surg.* 2024;111(2):1988–1994.
doi: 10.1097/js9.0000000000002194
- Liu H, Li X, Sun Y, *et al.* Eosinophilia-related adverse events reporting associated with medications: a disproportionality and regression analysis of the FDA Adverse Event Reporting System. *Int J Clin Pharm.* 2026.
doi: 10.1007/s11096-026-02109-z
- Ayuketang FA, Jäger U. Management of Cytokine Release Syndrome (CRS) and HLH. In: *The EBMT/EHA CAR-T Cell Handbook*. Springer International Publishing; 2022:135-139.
doi: 10.1007/978-3-030-94353-0_26
- Li J, Wang Y, Yang X, Zhu H, Jiang Z. Drug-induced hypoglycemia: a disproportionality analysis of the FAERS database. *Expert Opin Drug Saf.* 2024;23(8):1061–1067.
doi: 10.1080/14740338.2023.2278700
- Lakhan SE. Early Evaluation of the Food and Drug Administration (FDA) Adverse Event Monitoring System (AEMS): An Analysis of Over 32 Million Pharmacovigilance Reports. *Cureus.* 2026;18(4):e106259.

- doi: 10.7759/cureus.106259
21. Duggirala HJ, Tonning JM, Smith E, *et al.* Use of data mining at the Food and Drug Administration. *J Am Med Inform Assoc.* 2016;23(2):428–434.
doi: 10.1093/jamia/ocv063
 22. Böhm R, Bulin C, Waetzig V, Cascorbi I, Klein HJ, Herdegen T. Pharmacovigilance-based drug repurposing: The search for inverse signals via OpenVigil identifies putative drugs against viral respiratory infections. *Br J Clin Pharmacol.* 2021;87(11):4421–4431.
doi: 10.1111/bcp.14868
 23. Li Z, Zhu N, Liu Y, *et al.* A disproportionality analysis of real-world events from the FDA Adverse Event Reporting System (FAERS) for Atezolizumab. *BMC Pharmacol Toxicol.* 2025;26(1):51.
doi: 10.1186/s40360-025-00879-2
 24. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf.* 1999;20(2):109–117.
doi: 10.2165/00002018-199920020-00002
 25. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiol Drug Saf.* 2009;18(6):427–436.
doi: 10.1002/pds.1742
 26. Caster O, Aoki Y, Gattepaille LM, Grundmark B. Disproportionality Analysis for Pharmacovigilance Signal Detection in Small Databases or Subsets: Recommendations for Limiting False-Positive Associations. *Drug Saf.* 2020;43(5):479–487.
doi: 10.1007/s40264-020-00911-w
 27. Ooba N, Kubota K. Selected control events and reporting odds ratio in signal detection methodology. *Pharmacoepidemiol Drug Saf.* 2010;19(11):1159–1165.
doi: 10.1002/pds.2014
 28. Liang Q, Liao X, Wu H, Huang Y, Liang T, Li H. Real-world study of adverse events associated with gepant use in migraine treatment based on the VigiAccess and U.S. Food and Drug Administration's adverse event reporting system databases. *Front Pharmacol.* 2024;15:1431562.
doi: 10.3389/fphar.2024.1431562
 29. Li Z, Zhou Z, Zhang N, *et al.* Hepatitis associated with immune checkpoint inhibitors-based combinations of other therapies: A real-world pharmacovigilance analysis based on the FDA adverse event reporting system (FAERS) database. *Cancer Immunol Immunother.* 2024;74(1):25.
doi: 10.1007/s00262-024-03858-4
 30. Cobb DA, Lee DW. Cytokine Release Syndrome Biology and Management. *Cancer J.* 2021;27(2):119–125.
doi: 10.1097/ppo.0000000000000515
 31. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin.* 2023;73(1):17–48.
doi: 10.3322/caac.21763
 32. Rodet N, Zahed H, Colombet M, Bray F, McCormack V. Understanding age and sex differentials in cancer incidence and mortality: An international population-based study. *Int J Cancer.* 2026;158(8):2102–2110.
doi: 10.1002/ijc.70244
 33. Chan AC, Martyn GD, Carter PJ. Publisher Correction: Fifty years of monoclonals: the past, present and future of antibody therapeutics. *Nat Rev Immunol.* 2025.
doi: 10.1038/s41577-025-01261-3
 34. Strohl WR. Structure and function of therapeutic antibodies approved by the US FDA in 2023. *Antib Ther.* 2024;7(2):132–156.
doi: 10.1093/abt/tbae007
 35. Tanaka T, Narazaki M, Kishimoto T. Interleukin (IL-6) Immunotherapy. *Cold Spring Harb Perspect Biol.* Aug 1 2018;10(8):a028456.
doi: 10.1101/cshperspect.a028456
 36. Martín-Antonio B. Editorial: Understanding the Cytokine Release Syndrome: Toward Improving Cancer Immunotherapy. *Front Immunol.* 2021;12:666703.
doi: 10.3389/fimmu.2021.666703
 37. Aggarwal BB, Gupta SC, Kim JH. Historical perspectives on tumor necrosis factor and its superfamily: 25 years later, a golden journey. *Blood.* 2012;119(3):651–665.
doi: 10.1182/blood-2011-04-325225
 38. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, *et al.* Cytokine release syndrome. *J Immunother Cancer.* 2018;6(1):56.
doi: 10.1186/s40425-018-0343-9
 39. Liu Y, Jia YX, Li TT. Zhong liu mian yi zhi liao suo zhi xi bao yin zi shi fang zong he zheng de yan jiu jin zhan [Research progress on cytokine release syndrome due to tumor immunotherapy]. *Chinese Journal of Cancer Prevention and Treatment.* 2022;14(05):575–580. [In Chinese]
 40. Gkrinia EMM, Belančić A, Janković SM. Putting FAERS data into perspective: cautionary considerations for comparative safety assessment. *Eur J Hosp Pharm.* 2026.
doi: 10.1136/ejhpharm-2026-005052