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Risk of drug-induced pericardial effusion: a disproportionality analysis of the FAERS database

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Abstract

Objective By using the FAERS database, we aim to identify and assess risk signals of adverse drug events (ADEs) potentially causing pericardial effusion, to inform clinical drug management and promote rational drug use.

Methods We obtained reports of pericardial effusion events from the FAERS database spanning from the first quarter of 2004 to the second quarter of 2024, and identified the top 50 drugs ranked by report frequency or signal strength. Four algorithms, namely the reported odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS), were employed for signal detection of these drugs. Furthermore, for drugs with positive signals, we conducted sensitivity analyses and employed the Weibull shape parameter test to perform a time to onset (TTO) analysis.

Results We identified 20,057 ADEs related to pericardial effusion, involving 19,693 patients for analysis. The patient population comprised 10,187 males (51.7%) and 7,939 females (40.3%). Adults aged 18–65 years were the largest group (7,798 cases, 39.6%). Regarding clinical outcomes, 9,924 patients (50.4%) experienced hospitalization, and 2,770 cases (14.1%) resulted in death. Ranked by the ROR risk signal strength, the top 3 drugs were hydralazine [ROR (95% CI): 27.11 (22.28–33)], dasatinib [ROR (95% CI): 15.62 (14.07–17.33)], and mesalazine [ROR (95% CI): 8.99 (6.84–11.8)]. We conducted a TTO analysis for the 26 drugs with positive signals. The median TTO and interquartile range (IQR) for the top 3 drugs causing the earliest pericardial effusion were: cytarabine 14 (7.5,38), selexipag 14.5 (4.25, 157.75), dabigatran etexilate 29 (9, 229). Most drugs exhibited an early failure type.

Conclusion This study systematically compiled a list of drugs with potential risks of causing pericardial effusion. There is a significant association between pericardial effusion and the use of hydralazine, dasatinib, and mesalazine. Moreover, pericardial effusion is more common in patient groups receiving treatments with antineoplastic and immunomodulating agents.

Keywords Pericardial effusion, FDA, FAERS, Adverse drug events, Pharmacovigilance

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Introduction

The pericardium is a conical, serous sac consisting of a visceral and a parietal layer. Pericardial effusion (PE) occurs when the fluid accumulation within the pericardial cavity exceeds 50 mL [1]. As a common clinicopathological phenomenon, the reported prevalence of PE is up to 9% when it is diagnosed by echocardiography [2]. The severity of PE is correlated with the effusion volume. Minor effusion generally has minimal impact on hemodynamics, while significant effusion can lead to cardiac tamponade, posing a serious threat to life [3]. The etiology of PE is multifaceted, often attributed to factors such as inflammation, autoimmune diseases, and tumors. However, drug-induced pericardial effusion (DPE) is frequently overlooked as a potential causative factor [4–6]. DPE often complicates the treatment of the underlying disease and may impede its progress. For example, minoxidil, a common treatment for refractory hypertension, can cause PE as a severe side effect, leading to dyspnea and chest pain [7]. Due to DPE's significant latency, prompt diagnosis and intervention are crucial to prevent PE recurrence. Excessive fluid accumulation in the pericardial cavity severely impairs diastolic and systolic heart functions, potentially leading to serious adverse events such as hypotension and cardiac arrest [8]. Therefore, rapid and accurate identification of drug factors causing PE is crucial for optimizing treatment outcomes and enhancing patients' clinical prognosis.

The U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) is a publicly available, voluntary system, for post-marketing safety surveillance of FDA - approved drugs, facilitating the detection of potential links between drugs and adverse drug events (ADEs) [9]. Numerous scholars have uncovered the drug-associated factors underlying the onset of myocarditis [10], angioedema [11], and arrhythmia [12] by leveraging the FAERS database. This has effectively demonstrated the feasibility of drug-related study using the FAERS database. To date, various drugs, including immunosuppressants [13], antineoplastic agents [14], anticoagulants [15], and antihypertensive drugs [16], have been reported potentially to induce PE. However, the current related study has several limitations. On one hand, the data sources are predominantly case reports, lacking large-scale data. Consequently, the sample size is small and the representativeness is insufficient, making it difficult to comprehensively and accurately reflect the association between drugs and PE. On the other hand, there is a lack of systematic summarization of these drugs that induce PE. Current study fails to elaborate on the specific frequencies of drugs inducing PE and the strength of risk signals, thus being unable to provide adequate guidance for clinical medication. Compared with previous studies, this study relies on the advantages of large-scale and diverse data in the FAERS database, effectively overcoming the limitation of insufficient sample size. It also integrates the study results of predecessors to strengthen the evidence base. By adopting the disproportionality analysis method commonly used in the field of pharmacovigilance, this study accurately identifies the risk signals of drugs causing PE, provides references for clinical drug management and rational drug use, and reduces the risk of PE events in patients.

Materials and methods

Data source

The data for this study were sourced from the FAERS database, which has been publicly accessible and updated quarterly since 2004. The data were stored in ASCII or XML format (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). We acquired ASCII data spanning 82 quarters, from the first quarter of 2004 to the second quarter of 2024. The dataset includes patient demographics (DEMO), indication (INDI), drug use records (DRUG), therapy duration (THER), adverse event records (REAC), and patient outcomes (OUTC).

Data processing

The 82 quarterly data files were imported into a MySQL 8.0 database for processing. ① SQL queries were employed to eliminate duplicate entries in the DEMO table. In accordance with FDA recommendations, only the data with the most recent report date (FDA_DT) were retained for each unique case number (CASEID). In cases where both CASEID and FDA_DT were identical, the report with the highest PRIMARYID was selected. Subsequently, the DEMO table was linked to other subfiles to create a summary table (Supplementary Material 1). Since the FAERS database allows for multiple ADEs to be recorded per patient, which may potentially result in multiple distinct clinical outcomes for each individual, we selected the most severe clinical outcome as the definitive outcome for this study. ② The drug names were normalized using Medex_UIMA_1.3.8 from Vanderbilt University. The 'DRUG' table was de-duplicated, each drug was numbered, and the result was saved as DRUGNAME.txt. Special characters such as "#", "()", "[]" were removed during the pre-processing step to prepare for Medex_UIMA_1.3.8 mapping. To ensure the software operates properly, one should install a Java environment and correctly configure the environment variables for Java command recognition. Then, unzip the downloaded Medex_UIMA_1.3.8 to a local disk, define it as MedEx_HOME, and save the pre-processed DRUGNAME.txt in its input folder as the identification source file. Run the Java command to start the software. It reads DRUGNAME.txt in the input folder for drug name recognition, it compares with the built-in standard drug

dictionary, converts brand names and abbreviations to generic names, and outputs the results as an XML file to the output folder. ③ For drug classification, we adopted the Anatomical Therapeutic Chemical (ATC) classification system (https://www.who.int/tools/atc - ddd - tool kit/atc - classification), which is developed and regularly updated by the WHO Collaborating Centre for Drug Statistics Methodology.

By consulting the Medical Dictionary for Regulatory Activities (MedDRA) (https://www.meddra.org/), we designated "pericardial effusion" (code: 10034474) as the preferred term. Using this term, we searched for pertinent ADE reports. During the data processing phase, only reports with complete data were included in the analysis. Meanwhile, data points with an age greater than 120 years and a body weight exceeding 400 kg were defined as outliers and excluded. Given the wide-ranging sources of reports in the FAERS database, to effectively mitigate bias, the report sources were divided into two subsets: consumers and medical workers, for subsequent analysis. On this basis, a list of drugs potentially inducing PE was compiled. Depending on the magnitude of each drug's impact on PE formation, the drugs were classified into three categories: primary suspect (PS), secondary suspect, and concomitant or interaction. To guarantee the accuracy of conclusions, only ADEs in which PS drugs induced PE were incorporated into the analysis. The PS drugs were subsequently ranked according to their frequency and signal strength. Finally, during the analysis of the time to onset (TTO) of ADEs, reports lacking either "START_DT" or "END_DT", as well as those where "START_DT" was later than "EVENT_DT"', were excluded to ensure the validity of the analysis.

Statistic analysis

The disproportionality analysis and Bayesian approaches are pivotal analytical tools in pharmacovigilance. Within the framework of a 2 × 2 table (Table 1), the disproportionality analysis employs two algorithms: the reported odds ratio (ROR) and the proportional reported odds ratio (PRR) [17]. The Bayesian approaches primarily encompass two representative algorithms: the Bayesian confidence propagation neural network (BCPNN) [18] and the multi-item gamma Poisson shrinker (MGPS) [19]. The formulas for these four algorithms are provided in Supplementary Material 2. To enhance the reliability of the drug-ADE correlation analysis, an ADE signal is generated only when criteria from all four algorithms are concurrently met. The ROR algorithm is simple and can intuitively present the association between drugs and ADEs. In contrast, the PRR algorithm highlights differences by calculating ratios, enabling the efficient screening of drugs with abnormal risk signals. The BCPNN, based on Bayesian principles, integrates diverse data and supports cross validation, thereby enhancing signal robustness. The MGPS effectively controls biases caused by data sparsity or over reporting [20]. Furthermore, the FAERS database compiles spontaneous ADEs from diverse populations. Given the notable disparities in medical expertise between consumers and medical workers, this discrepancy may introduce false positive signals into the dataset. To assess and quantify this potential effect, we conducted a sensitivity analysis.

We used the median and interquartile range (IQR) as key statistics to describe the TTO. To further explore the distribution characteristics of the TTO, we applied the Weibull shape parameter (WSP) test [21] to reveal its characteristics. The WSP test serves as an early - warning indicator by detecting ADEs in patients during specific periods, which enables prompt preventive measures or adjustments to treatment plans. All statistical analyses were conducted using R software.

Table 1 Four-fold table of disproportionality analysis

Item	Number of target adverse event reports	Number of other adverse event reports	Total
Target drug	a	b	a + b
Other drugs	c	d	c + d
Total	a + c	b + d	N = a + b + c + d

a, number of reports containing both the target drug and target adverse reaction reports; b, number of reports containing other adverse reaction reports of the target drug; c, number of reports containing the target adverse reaction reports of other drugs; d, number of reports containing other drugs and other adverse reaction reports; N, the number of reports

Outcomes

Retrieval process

We retrieved a total of 53,769,390 ADEs from the FAERS database, and 20,057 of them were associated with PE. Subsequently, after data processing, 19,693 patients were included in the baseline analysis. The detailed workflow is presented in Fig. 1.

Basic characteristics of ADE reports related to pericardial effusion

Regarding gender distribution, males accounted for a higher proportion (51.7%) than females (40.3%). Across different age groups, adults aged 18–65 years made up the largest proportion (39.6%), followed by elderly patients (27.5%). The ADE reports mostly came from medical workers. Basic information is shown in Table 2.

From 2004 to 2024, the number of ADE reports related to PE showed an overall upward trend (Fig. 2A). Significantly, since 2012, this number has surged and maintained a high level. The peak occurred in 2023, with 1757 cases reported. The reduced number of ADE reports in 2024 is attributable to the inclusion of data from only two quarters.

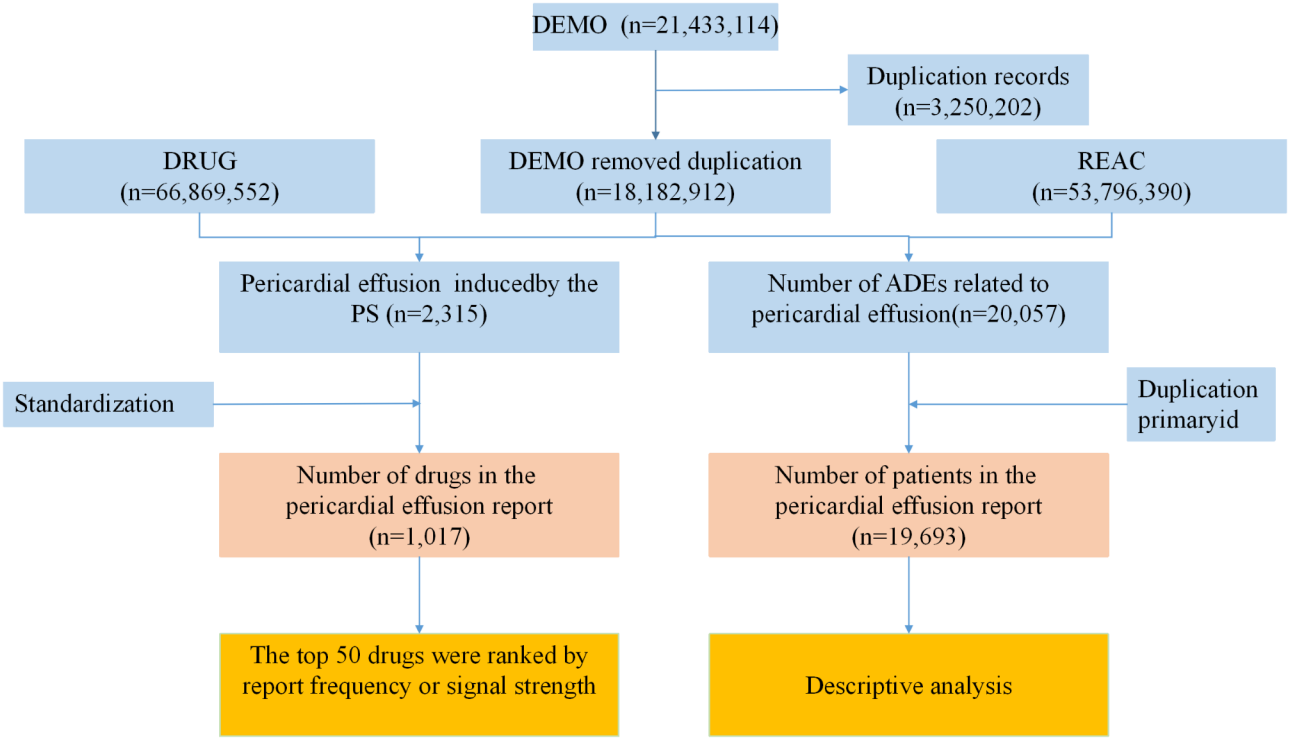


Fig. 1 Flowchart for identifying pericardial effusion reports. ADE: adverse drug event; PS: primary suspect

Table 2 Clinical characteristics of pericardial effusion report

Dimension	Classification	Number of reports	Percent(%)
Sex			
	Female	10,193	51.7
	Male	7940	40.3
	Missing	1560	8.0
Age (Year)			
	< 18	843	4.3
	18–65	7798	39.6
	≥ 65	5424	27.5
	Missing	5628	28.6
Report source			
	Physician	6928	35.2
	Consumer	5394	27.4
	Other health perfessional	3002	15.2
	Health perfessional	2165	11.0
	Pharmacist	1019	5.2
	Missing	1047	5.3
	Lawyer	128	0.6
	Registered Nurse	10	0.1

The majority of ADE reports came from European and American countries. The top 8 countries with the most ADE reports were the United States (9380 cases), Japan (1186 cases), Canada (1136 cases), Germany (981 cases), France (977 cases), the United Kingdom (774 cases), Italy (388 cases), and China (379 cases). For details, see Fig. 2B.

As depicted in Fig. 2C, the distribution of patient outcomes is presented as follows. Hospitalization was the most frequent clinical outcome, with 9924 cases (50.4%). Moreover, 2770 cases (14.1%) resulted in death. The top 5 drugs that led to hospitalization and death outcomes are listed in Table 3.

Top 50 drugs based on report frequency

By analyzing ADE reports, we identified the top 50 PS drugs based on reporting frequency. These drugs include: adalimumab (436 cases, 2.21%), ibrutinib (383 cases, 1.94%), treprostinil (375 cases, 1.90%), clozapine (374 cases, 1.90%), dasatinib (363 cases, 1.84%), nivolumab (339 cases, 1.72%), ambrisentan (325 cases, 1.67%), sacubitril/valsartan (299 cases, 1.52%), macitentan (297 cases, 1.51%), dabigatran etexilate (286 cases, 1.45%), lenalidomide (281 cases, 1.43%), rivaroxaban (264 cases, 1.34%), infliximab (243 cases, 1.23%), bosentan (239 cases, 1.21%), rosiglitazone (234 cases, 1.19%), among others (see Table 4 for details). It is noteworthy that the relatively high ranking of certain drugs among those causing PE may be due to their high usage volume. This does not necessarily mean that there is an inevitable link between these drugs and PE. According to the Anatomical Therapeutic Chemical (ATC) classification, the top 50 drugs are categorized as follows: antineoplastic and

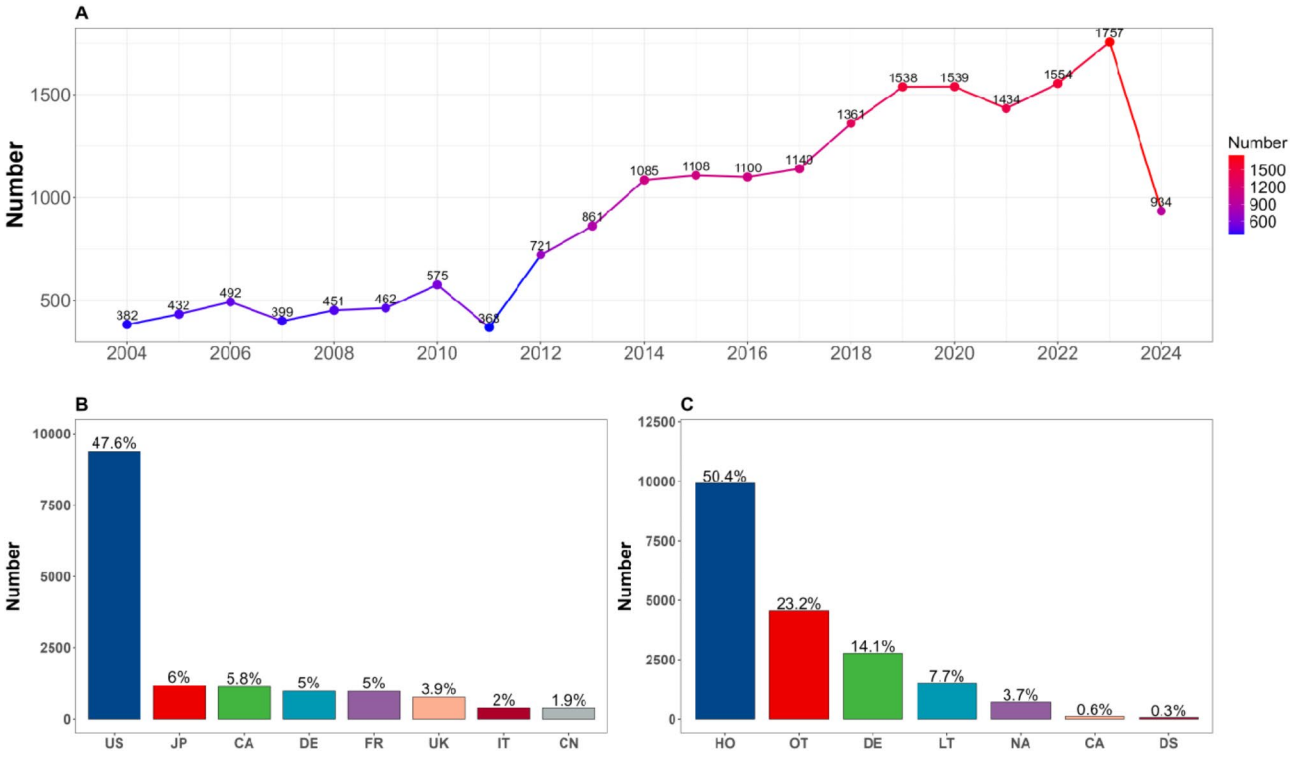


Fig. 2 (**A**) Annual number of reported adverse drug events related to pericardial effusion. (**B**) Proportion of clinical outcomes. CA: congenital anomaly, DE: death, DS: disability, HO: hospitalization, LT: life-threatening, OT: other, NA: not available. (**C**) Top 8 reporting countries. CA: Canada, CN: China, DE: Germany, FR: France, IT: Italy, JP: Japan, UK: The United Kingdom, US: The United States

Table 3 Top 5 drugs with case outcome of hospitalization and death

No.	Hospitalization			Death		
	Drug name	Number of reports	Percent (%)	Drug name	Number of reports	Percent (%)
1	Treprostinil	269	2.7	Macitentan	81	2.9
2	Adalimumab	258	2.5	Bosentan	78	2.8
3	Ibrutinib	252	2.5	Treprostinil	50	1.8
4	Ambrisentan	228	2.2	Nivolumab	48	1.7
5	Clozapine	213	2.1	Erlotinib	46	1.6

immunomodulating agents (31 drugs), cardiovascular system drugs (11 drugs), blood system drugs (3 drugs), alimentary tract and metabolism drugs (3 drugs), musculo - skeletal system drug (1 drug), and nervous system drug (1 drug).

Disproportionality analysis and sensitivity analysis

Signal detection was conducted on the top 50 PS drugs, resulting in the identification of 26 drugs as positive signals (Fig. 3). The results showed that: hydralazine [ROR (95% CI): 27.11 (22.28-33)], dasatinib [ROR (95% CI): 15.62 (14.07–17.33)], mesalazine [ROR (95% CI): 8.99 (6.84–11.8)], epoprostenol [ROR (95% CI): 8.97 (4.79–10.74)], bosutinib [ROR (95% CI): 8.34 (6.45–10.78)], crizotinib [ROR (95% CI): 8.25 (6.73–10.11)], macitentan [ROR (95% CI): 7.44 (6.63–8.35)], gemcitabine [ROR (95% CI): 6.54 (5.65–7.57)], dabigatran etexilate [ROR (95% CI): 6.46 (5.79–7.21)], bosentan [ROR (95% CI): 5.53 (4.69–6.05)], nivolumab [ROR (95% CI): 5.29 (4.75–5.89)], atezolizumab [ROR (95% CI): 5.19 (4.27–6.3)], ibrutinib [ROR (95% CI): 5.06 (4.58–5.6)], selexipag [ROR (95% CI): 4.97 (4.16–5.94)], nilotinib [ROR (95% CI): 4.82 (4.13–5.64)], trastuzumab [ROR (95% CI): 4.71 (4.14–5.37)], osimertinib [ROR (95% CI): 4.6 (3.64–5.81)], cytarabine [ROR (95% CI): 4.4 (3.52–5.5)], pembrolizumab [ROR (95% CI): 4.29 (3.76–4.9)], ambrisentan [ROR (95% CI): 4.22 (3.78–4.71)], imatinib [ROR (95% CI): 4.22 (3.71–4.79)], clozapine [ROR (95% CI): 4.16 (3.76–4.61)], everolimus [ROR (95% CI): 3.9 (3.37–4.51)], rosiglitazone [ROR (95% CI): 3.64 (3.2–4.14)], treprostinil [ROR (95% CI): 3.57 (3.23–3.96)]. Among these 26 drugs, 7 drugs (dasatinib, mesalazine, bosutinib, nilotinib, trastuzumab, pembrolizumab, imatinib) have documented expected adverse reactions of PE in FDA - approved drug labels,

Table 4 Basic information and classification of the top 50 drugs based on report frequency

No.	Drug	Frequency	Percentage (%)	Classification
1	Adalimumab	436	2.21%	L
2	Ibrutinib	383	1.94%	L
3	treprostinil	375	1.90%	C
4	Clozapine	374	1.90%	N
5	Dasatinib	363	1.84%	L
6	Nivolumab	339	1.72%	L
7	Ambrisentan	325	1.67%	C
8	Sacubitril/valsartan	299	1.52%	C
9	Macitentan	297	1.51%	C
10	Dabigatran etexilate	286	1.45%	B
11	Lenalidomide	281	1.43%	L
12	Rivaroxaban	264	1.34%	B
13	Infliximab	243	1.23%	L
14	Bosentan	239	1.21%	C
15	Rosiglitazone	234	1.19%	A
16	Etanercept	225	1.14%	L
17	Pembrolizumab	221	1.12%	L
18	Trastuzumab	202	1.03%	L
19	Apixaban	199	1.01%	B
20	Imatinib	196	1.00%	L
21	Methotrexate	191	0.97%	L
22	Gemcitabine	182	0.92%	L
23	Everolimus	180	0.91%	L
24	Tacrolimus	166	0.84%	L
25	Rituximab	157	0.80%	L
26	Nilotinib	155	0.78%	L
27	Sunitinib	148	0.75%	L
28	Bevacizumab	135	0.68%	L
29	Erlotinib	125	0.63%	L
30	Rofecoxib	124	0.63%	L
31	Selexipag	122	0.62%	C
32	Epoprostenol	116	0.59%	C
33	Carboplatin	106	0.54%	L
34	Mesalazine	104	0.53%	A
35	Hydralazine	102	0.52%	C
36	Eculizumab	95	0.48%	L
37	Amlodipine	92	0.47%	C
38	Digoxin	88	0.45%	C
39	Crizotinib	88	0.45%	L
40	Minoxidil	87	0.44%	C
41	Zoledronic acid	85	0.43%	M
42	Atezolizumab	74	0.38%	L
43	Peginterferon beta-1a	74	0.38%	L
44	Palbociclib	73	0.37%	L
45	Ondansetron	72	0.37%	A
46	Osimertinib	71	0.36%	L
47	Mycophenolate mofetil	67	0.34%	L
48	Cytarabine	65	0.33%	L
49	Bosutinib	64	0.32%	L
50	Venetoclax	62	0.31%	L

A: alimentary tract and metabolism drugs, B: blood system drugs, C: cardiovascular system drugs, L: antineoplastic and immunomodulating agents, M: musculo-skeletal system drugs, N: nervous system drugs

while the remaining 19 drugs do not mention the risk of inducing PE. Physicians should intensify the monitoring of PE symptoms in patients using these drugs. This includes regular echocardiographic examinations and close observation of whether patients exhibit symptoms such as dyspnea, chest pain, and palpitations, enabling the early detection and timely management of potential adverse reactions.

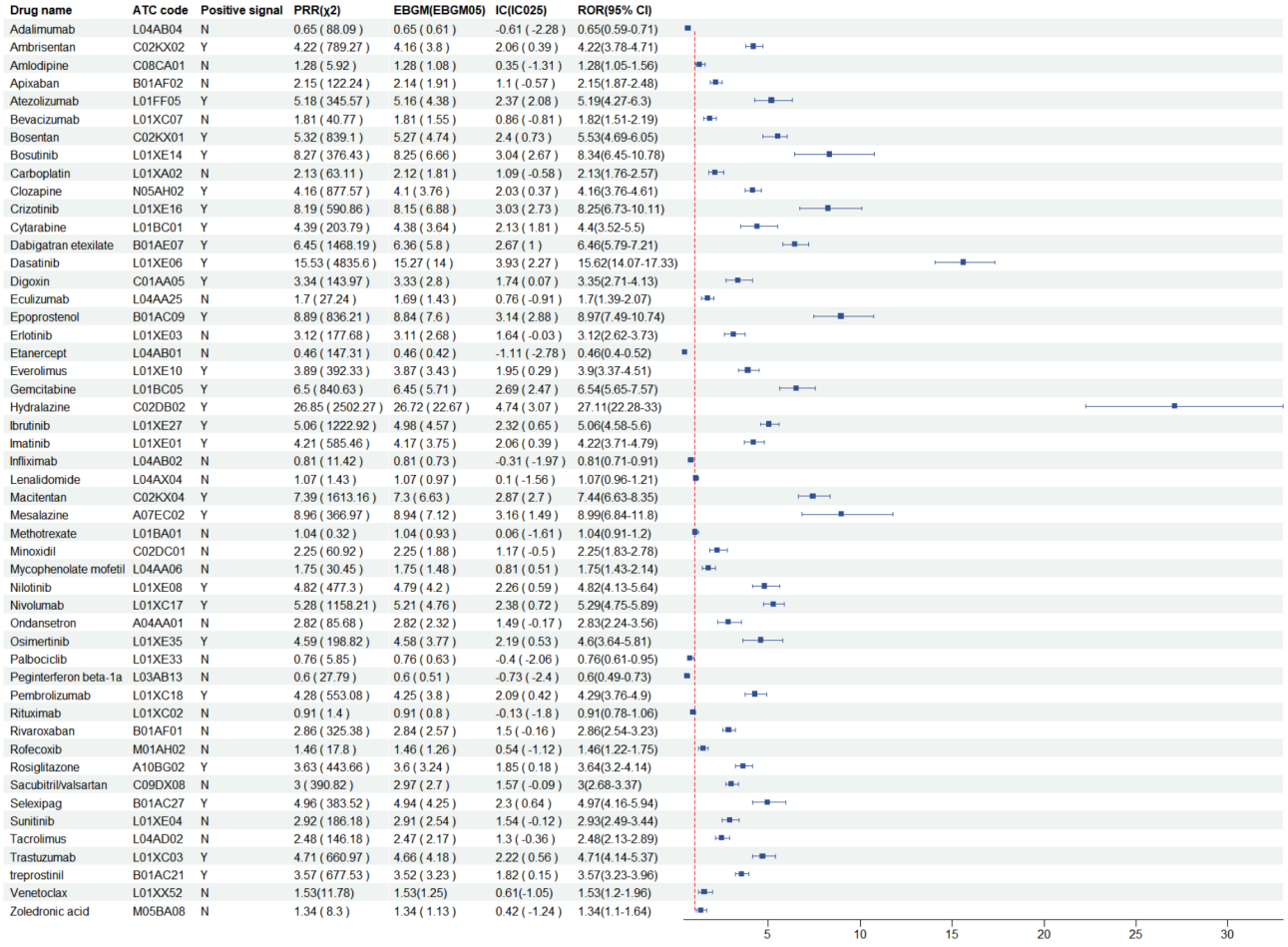
The data in the FAERS database come from diverse sources, including spontaneous reports submitted by both consumers (patients and other related individuals) and medical workers (physicians, pharmacists, and other health specialists). There may be significant differences between these two types of reporters in terms of professional knowledge, reporting motivations, and report content. By conducting sensitivity analyses, we can reduce biases arising from these varied data sources, thereby enhancing the precision and reliability of our analyses. We used the ROR method for a disproportionality analysis of ADEs reported by consumers and medical workers for the 26 positive drugs. The results are shown in Fig. 4. For some drugs, such as ambrisentan [ROR (95% CI): 0.74 (0.57–0.83)] and digoxin [ROR (95% CI): 0.37 (0.16–0.87)], ADEs were more frequently reported by consumers, and the results are not reliable. However, ADEs for the majority of drugs were predominantly reported by medical workers, lending stability to the results.

Time-to-onset analysis

When analyzing the TTO of the 26 drugs that generated positive signals (Table 5), we used the WSP test and focused specifically on the top 10 drugs that induced PE in the shortest time. The median TTO and IQR of these drugs are presented as follows: cytarabine 14 (7.5, 38); selexipag 14.5 (4.25, 157.75); dabigatran etexilate 29 (9, 229); pembrolizumab 29 [11, 68]; osimertinib 32 (11.75, 107); clozapine 34 (16, 1623); crizotinib 40 (26, 108.5); atezolizumab 55 (18, 128); nivolumab 59.5 (26.75, 138.5); everolimus 60 (21, 195). The results of the WSP analysis showed that the shape parameter β and the upper limit of its 95% CI for most drugs were less than 1, indicating that the probability of these drugs inducing PE tends to decrease over time.

Top 50 drugs based on signal strength

Using reporting frequency as the inclusion criterion for drugs may introduce potential biases. To address this shortcoming, we used disproportionality analysis to rank the top 50 drugs according to signal strength. This strategy can help identify potential safety issues independent of drug use frequency and enables focused monitoring of drugs with high-risk signals. The results are shown in Fig. 5. Specifically, the top 10 drugs are as follows: pergolide [ROR (95% CI): 35.97(20.2–64.05)],



Drug name	ATC code	Positive signal	PRR(χ2)	EBGM(EBGM05)	IC(IC025)	ROR(95% CI)
Adalimumab	L04AB04	N	0.65 (88.09)	0.65 (0.61)	-0.61 (-2.28)	0.65(0.59-0.71)
Ambrisentan	C02KX02	Y	4.22 (789.27)	4.16 (3.8)	2.06 (0.39)	4.22(3.78-4.71)
Amlodipine	C08CA01	N	1.28 (5.92)	1.28 (1.08)	0.35 (-1.31)	1.28(1.05-1.56)
Apixaban	B01AF02	N	2.15 (122.24)	2.14 (1.91)	1.1 (-0.57)	2.15(1.87-2.48)
Atezolizumab	L01FF05	Y	5.18 (345.57)	5.16 (4.38)	2.37 (2.08)	5.19(4.27-6.3)
Bevacizumab	L01XC07	N	1.81 (40.77)	1.81 (1.55)	0.86 (-0.81)	1.82(1.51-2.19)
Bosentan	C02KX01	Y	5.32 (839.1)	5.27 (4.74)	2.4 (0.73)	5.53(4.69-6.05)
Bosutinib	L01XE14	Y	8.27 (376.43)	8.25 (6.66)	3.04 (2.67)	8.34(6.45-10.78)
Carboplatin	L01XA02	N	2.13 (63.11)	2.12 (1.81)	1.09 (-0.58)	2.13(1.76-2.57)
Clozapine	N05AH02	Y	4.16 (877.57)	4.1 (3.76)	2.03 (0.37)	4.16(3.76-4.61)
Crizotinib	L01XE16	Y	8.19 (590.86)	8.15 (6.88)	3.03 (2.73)	8.25(6.73-10.11)
Cytarabine	L01BC01	Y	4.39 (203.79)	4.38 (3.64)	2.13 (1.81)	4.4(3.52-5.5)
Dabigatran etexilate	B01AE07	Y	6.45 (1468.19)	6.36 (5.8)	2.67 (1)	6.46(5.79-7.21)
Dasatinib	L01XE06	Y	15.53 (4835.6)	15.27 (14)	3.93 (2.27)	15.62(14.07-17.33)
Digoxin	C01AA05	Y	3.34 (143.97)	3.33 (2.8)	1.74 (0.07)	3.35(2.71-4.13)
Eculizumab	L04AA25	N	1.7 (27.24)	1.69 (1.43)	0.76 (-0.91)	1.7(1.39-2.07)
Epoprostenol	B01AC09	Y	8.89 (836.21)	8.84 (7.6)	3.14 (2.88)	8.97(7.49-10.74)
Erlotinib	L01XE03	N	3.12 (177.68)	3.11 (2.68)	1.64 (-0.03)	3.12(2.62-3.73)
Etanercept	L04AB01	N	0.46 (147.31)	0.46 (0.42)	-1.11 (-2.78)	0.46(0.4-0.52)
Everolimus	L01XE10	Y	3.89 (392.33)	3.87 (3.43)	1.95 (0.29)	3.9(3.37-4.51)
Gemcitabine	L01BC05	Y	6.5 (840.63)	6.45 (5.71)	2.69 (2.47)	6.54(5.65-7.57)
Hydralazine	C02DB02	Y	26.85 (2502.27)	26.72 (22.67)	4.74 (3.07)	27.11(22.28-33)
Ibrutinib	L01XE27	Y	5.06 (1222.92)	4.98 (4.57)	2.32 (0.65)	5.06(4.58-5.6)
Imatinib	L01XE01	Y	4.21 (585.46)	4.17 (3.75)	2.06 (0.39)	4.22(3.71-4.79)
Infliximab	L04AB02	N	0.81 (11.42)	0.81 (0.73)	-0.31 (-1.97)	0.81(0.71-0.91)
Lenalidomide	L04AX04	N	1.07 (1.43)	1.07 (0.97)	0.1 (-1.56)	1.07(0.96-1.21)
Macitentan	C02KX04	Y	7.39 (1613.16)	7.3 (6.63)	2.87 (2.7)	7.44(6.63-8.35)
Mesalazine	A07EC02	Y	8.96 (366.97)	8.94 (7.12)	3.16 (1.49)	8.99(6.84-11.8)
Methotrexate	L01BA01	N	1.04 (0.32)	1.04 (0.93)	0.06 (-1.61)	1.04(0.91-1.2)
Minoxidil	C02DC01	N	2.25 (60.92)	2.25 (1.88)	1.17 (-0.5)	2.25(1.83-2.78)
Mycophenolate mofetil	L04AA06	N	1.75 (30.45)	1.75 (1.48)	0.81 (0.51)	1.75(1.43-2.14)
Nilotinib	L01XE08	Y	4.82 (477.3)	4.79 (4.2)	2.26 (0.59)	4.82(4.13-5.64)
Nivolumab	L01XC17	Y	5.28 (1158.21)	5.21 (4.76)	2.38 (0.72)	5.29(4.75-5.89)
Ondansetron	A04AA01	N	2.82 (85.68)	2.82 (2.32)	1.49 (-0.17)	2.83(2.24-3.56)
Osimertinib	L01XE35	Y	4.59 (198.82)	4.58 (3.77)	2.19 (0.53)	4.6(3.64-5.81)
Palbociclib	L01XE33	N	0.76 (5.85)	0.76 (0.63)	-0.4 (-2.06)	0.76(0.61-0.95)
Peginterferon beta-1a	L03AB13	N	0.6 (27.79)	0.6 (0.51)	-0.73 (-2.4)	0.6(0.49-0.73)
Pembrolizumab	L01XC18	Y	4.28 (553.08)	4.25 (3.8)	2.09 (0.42)	4.29(3.76-4.9)
Rituximab	L01XC02	N	0.91 (1.4)	0.91 (0.8)	-0.13 (-1.8)	0.91(0.78-1.06)
Rivaroxaban	B01AF01	N	2.86 (325.38)	2.84 (2.57)	1.5 (-0.16)	2.86(2.54-3.23)
Rofecoxib	M01AH02	N	1.46 (17.8)	1.46 (1.26)	0.54 (-1.12)	1.46(1.22-1.75)
Rosiglitazone	A10BG02	Y	3.63 (443.66)	3.6 (3.24)	1.85 (0.18)	3.64(3.2-4.14)
Sacubitril/valsartan	C09DX08	N	3 (390.82)	2.97 (2.7)	1.57 (-0.09)	3(2.68-3.37)
Selexipag	B01AC27	Y	4.96 (383.52)	4.94 (4.25)	2.3 (0.64)	4.97(4.16-5.94)
Sunitinib	L01XE04	N	2.92 (186.18)	2.91 (2.54)	1.54 (-0.12)	2.93(2.49-3.44)
Tacrolimus	L04AD02	N	2.48 (146.18)	2.47 (2.17)	1.3 (-0.36)	2.48(2.13-2.89)
Trastuzumab	L01XC03	Y	4.71 (660.97)	4.66 (4.18)	2.22 (0.56)	4.71(4.14-5.37)
treprostinil	B01AC21	Y	3.57 (677.53)	3.52 (3.23)	1.82 (0.15)	3.57(3.23-3.96)
Venetoclax	L01XX52	N	1.53(11.78)	1.53(1.25)	0.61(-1.05)	1.53(1.2-1.96)
Zoledronic acid	M05BA08	N	1.34 (8.3)	1.34 (1.13)	0.42 (-1.24)	1.34(1.1-1.64)

Fig. 3 Signal detection results of the top 50 drugs based on report frequency. ROR: the reporting odds ratio; PRR: the proportional reporting ratio; EBGM: the empirical Bayes geometric mean; EBGM05: the lower limit of 95% CI, of EBGM; IC: the information component; IC025: the lower limit of 95% CI, of the IC; Y: yes, N: no

arsenic trioxide [ROR (95% CI): 28.53(20.47–39.76)], loncastuximab tesirine [ROR (95% CI): 28.27(12.54–63.71)], hydralazine [ROR (95% CI): 27.11(22.28–33)], dinutuximab [ROR (95% CI): 22.71(11.26–45.81)], plerixafor [ROR (95% CI): 18.89(10.1–35.33)], ceritinib [ROR (95% CI): 17.44(13.06–23.28)], denileukin diftitox [ROR (95% CI): 15.85(5.06–49.62)], dasatinib [ROR (95% CI): 15.62(14.07–17.33)], porfimer [ROR (95% CI): 14.69(6.07–35.56)].We found that the number of antineoplastic and immunomodulating agents reached 34, accounting for a significant proportion (68%) among the top 50 drugs. These types of drugs remain important risk factors for the occurrence of PE.

Discussion

This is the first comprehensive signal-detection study using the FAERS database to investigate high-risk drugs potentially inducing PE. Consistent with previous studies [22], our results show that DPE events are predominantly concentrated in adult patients, especially males. Regarding clinical outcomes, 50.4% of patients were hospitalized, and 14.1% of patients even died. The data, mainly from medical workers' reports, are credible to some extent. Clinicians should be aware of the PE risk when prescribing drugs to adult males. The annual number of reported DPE events has been increasing, peaking at 1,757 cases. We performed signal detection on the top 50 drugs associated with PE using the ROR and PRR methods, and 26 drugs with positive signals were identified. Remarkably, only 7 of these drugs listed PE as an expected ADE in FDA - approved drug labels. Due to the complexity of drug development and clinical trials, ADE information in drug labels may not be updated promptly, which may lead to inadequate warnings and preventive measures for patients during drug use.

Adalimumab, a commonly used tumor necrosis factor-α blocker for rheumatoid arthritis and ankylosing spondylitis [23], is the drug most frequently associated with PE events in the FAERS database. Many studies [24–26] have documented PE events in patients

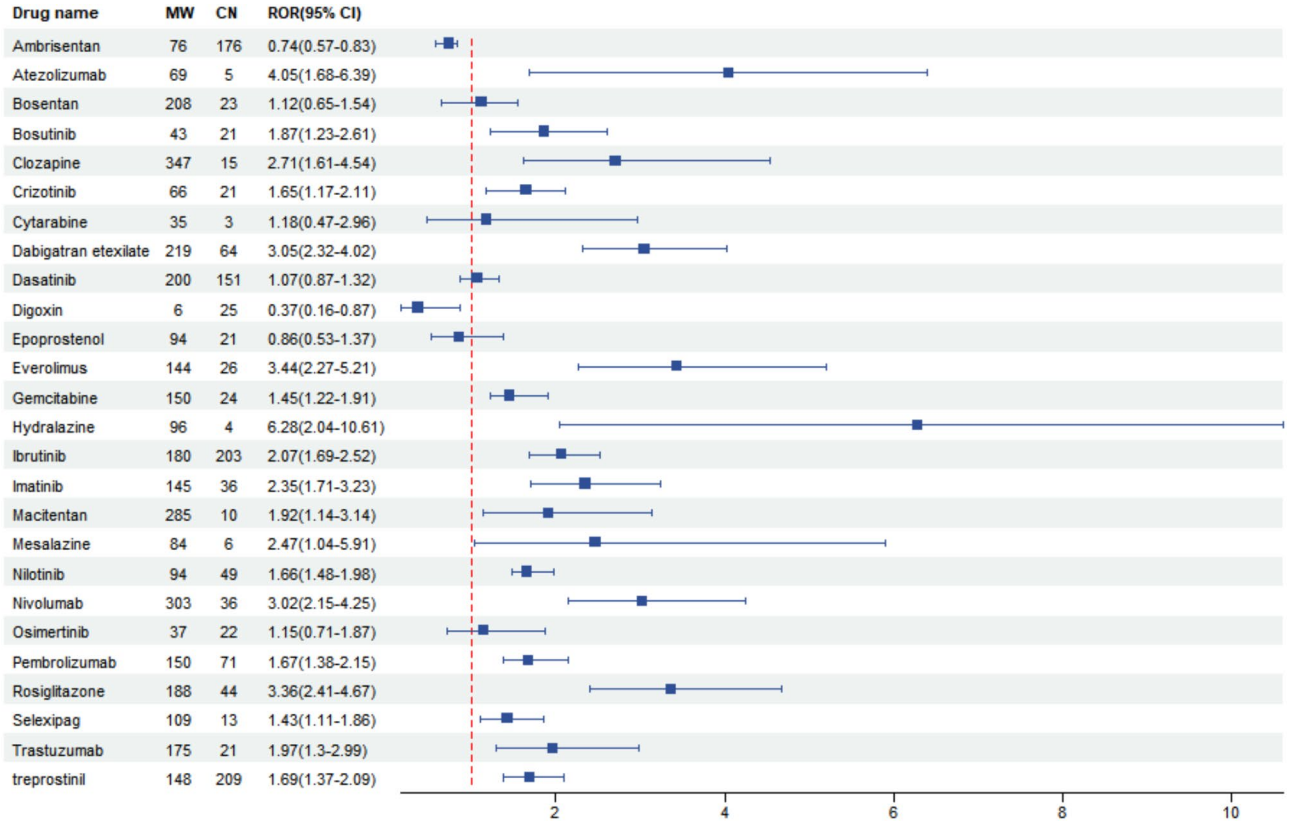


Fig. 4 Forest plot of sensitivity analysis of reporting odds ratios for the 26 positive drugs causing pericardial effusion. MW: medical worker; CN: consumer

undergoing adalimumab therapy. Despite being identified as a negative drug in pharmacovigilance signal detection, close monitoring for PE in patients using adalimumab remains essential, considering the patient's overall health and medication risks. Ibrutinib is linked to the highest number of ADEs of PE among drugs with positive signals. Ibrutinib, a novel targeted anticancer agent approved by FDA, is routinely employed in the treatment of mantle cell lymphoma and chronic lymphocytic leukemia [27]. Several clinical studies [28–30] have shown that ibrutinib can induce hemorrhagic PE. The underlying mechanism is postulated to involve its interference with platelet aggregation through inhibition of Bruton's tyrosine kinase and tyrosine kinase expressed in hepatocellular carcinoma; when administered concomitantly with antiplatelet and anticoagulant medications, the risk of hemorrhagic PE is substantially elevated [31, 32]. Utilizing the WSP test, this study determined that the median TTO for ibrutinib-induced PE is 80 days, and notably, the drug's package insert omits warning information regarding PE risk. This underscores the necessity for heightened vigilance and close monitoring of PE risk when initiating ibrutinib therapy in clinical practice [33].

The ROR serves as an index to assess the strength of the association between a drug and an ADE. A higher ROR indicates a stronger correlation between the drug and the onset of PE [34]. This study identified hydralazine, dasatinib, and mesalazine as the top 3 drugs with higher risk signals. Hydralazine exerts its hypotensive effect by targeting and relaxing vascular smooth muscles, thereby reducing peripheral resistance and lowering blood pressure. Moreover, it enhances cardiac output and optimizes cardiac function, leading to its widespread use in the treatment of hypertension and heart failure [35]. Recent study indicates that the PE caused by this drug is not due to direct cell toxicity, but rather closely linked to the mechanism of drug-induced lupus-like syndrome [36–38]. Further investigation reveals that this pathological process frequently involves autoimmune reactions triggered by the inhibition of T-cell DNA methylation and the accumulation of autoantibodies, particularly in patients with slow acetylation following hydralazine treatment [39]. Clinicians must maintain high vigilance in monitoring for signs of hydralazine-induced lupus-like syndrome (HILS), particularly in patients receiving doses of 200 milligrams or more daily for over three months. Any nonspecific symptoms or unexplained cases of PE should be viewed with a high index of suspicion for HILS, warranting immediate drug withdrawal [40, 41].

Dasatinib, a potent tyrosine kinase inhibitor, is primarily administered for targeted therapy in chronic myelogenous leukemia (CML) [42]. With rapid absorption,

Table 5 Analysis of time-to-onset of 26 positive signal drugs causing pericardial effusion

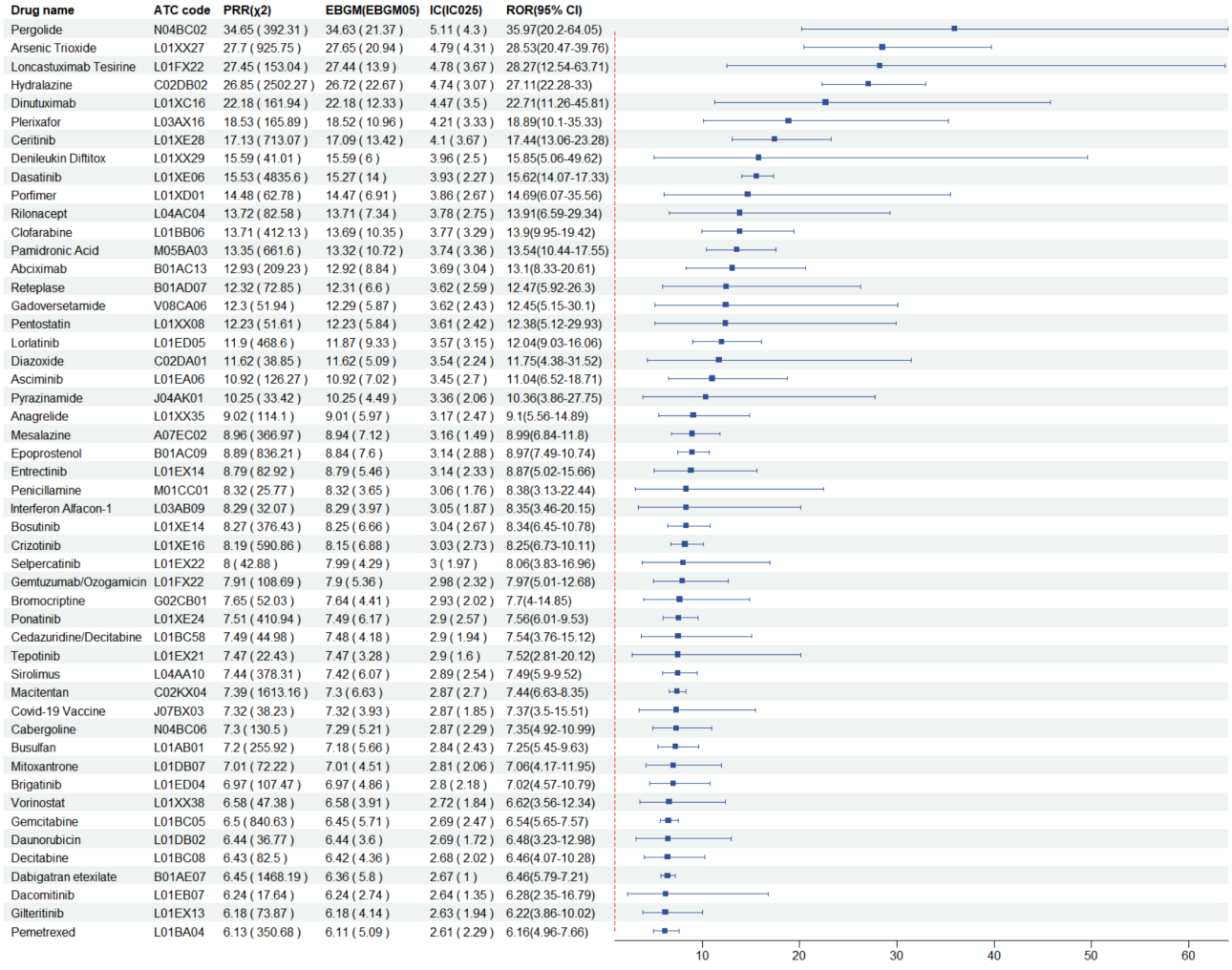
Drug	*n*	TTO	Scale parameter: α (95% CI)	Shape parameter: β (95% CI)	type
Ambrisentan#	96	589.5(232.25,1369)	835.80(630.51, 1041.09)	0.85(0.71, 0.99)	Early failure
Atezolizumab#	61	55(18,128)	96.75(64.16, 129.34)	0.80(0.65, 0.93)	Early failure
Bosentan#	105	223(98,955)	518.59(367.90, 669.29)	0.70(0.59, 0.80)	Early failure
Bosutinib	14	616.5(374.25,1034.25)	836.33(360.71, 1311.95)	0.96(0.55, 1.37)	Random Failure
Clozapine#	129	34(16,1623)	380.10(207.94, 552.27)	0.40(0.35, 0.46)	Early failure
Crizotinib#	24	40(26,108.5)	130.01(44.62, 215.40)	0.65(0.47, 0.83)	Early failure
Cytarabine#	27	14(7.5,38)	26.05(14.42, 37.69)	0.89(0.65, 1.14)	Random Failure
Dabigatran etexilate#	73	29(9,229)	105.87(54.17, 157.57)	0.50(0.41, 0.58)	Early failure
Dasatinib	89	155(43,516)	308.92(202.15, 415.69)	0.64(0.53, 0.74)	Early failure
Digoxin#	11	1624(392.5,3996)	1764.72(168.01, 3361.42)	0.68(0.33, 1.03)	Random Failure
Epoprostenol#	51	245(78,963)	539.53(260.64, 818.42)	0.56(0.44, 0.68)	Early failure
Everolimus#	91	60(21,195)	133.46(90.14, 176.78)	0.67(0.58, 0.77)	Early failure
Gemcitabine#	54	125(44.5,179)	140.06(103.20, 176.91)	1.06(0.83, 1.29)	Random Failure
Hydralazine#	3	239(126,267.5)	185.34(-23.58, 394.26)	1.05(-0.03, 2.21)	Random Failure
Ibrutinib#	80	186.5(80.5,455.25)	341.62(244.76, 438.48)	0.82(0.68, 0.95)	Early failure
Imatinib	71	96(31,885)	322.51(179.08, 465.93)	0.55(0.45, 0.65)	Early failure
Macitentan#	100	185.5(29.75,512.75)	297.80(210.66, 384.94)	0.71(0.60, 0.82)	Early failure
Mesalazine	12	91(23,150)	141.58(49.55, 233.61)	0.93(0.53, 1.32)	Random Failure
Nilotinib	54	106(22.5,619.25)	281.95(148.24, 415.66)	0.59(0.47, 0.72)	Early failure
Nivolumab#	164	59.5(26.75,138.5)	113.25(87.68, 138.81)	0.72(0.64, 0.80)	Early failure
Osimertinib#	22	32(11.75,107)	78.66(19.93, 137.39)	0.59(0.40, 0.78)	Early failure
Pembrolizumab	67	29(11,69)	57.27(38.37, 76.16)	0.77(0.63, 0.91)	Early failure
Rosiglitazone#	39	476(278.5,745.5)	657.72(456.12, 859.32)	1.08(0.82, 1.34)	Random Failure
Selexipag#	24	14.5(4.25,157.75)	56.87(11.64, 102.10)	0.53(0.37, 0.70)	Early failure
Trastuzumab	76	102(39.5,231.75)	191.70(131.04, 252.36)	0.75(0.63, 0.88)	Early failure
Treprostinil#	136	257(67,680)	440.28(328.74, 551.82)	0.70(0.61, 0.79)	Early failure

A number sign (#) denotes the absence of documented risk for pericardial effusion in the labels of FDA-approved drugs

dasatinib is primarily metabolized and eliminated through the cytochrome P450 (CYP) 3A4 enzyme system, with a half-life of about 3 to 4 h [43]. Studies indicate that dasatinib may induce severe PE in 1% of patients [6]. A clinical study of 102 CML patients treated with dasatinib revealed that 30.9% developed pericardial or pleural effusions [44]. Although the exact mechanism of dasatinib-induced PE remains unclear, studies suggest it may involve the drug's inhibition of platelet-derived growth factor receptor-β (PDGFR-β) or SRC family kinases, resulting in increased vascular permeability [45]. Moreover, an analysis of the correlation between drug dosage and ADEs revealed that CML patients receiving dasatinib at doses of 140 mg, 100 mg, or 50 mg were all susceptible to developing PE. Further analysis indicated that the TTO for dasatinib-induced PE is 155 days. In light of this finding, regular chest X-ray examinations are recommended for patients undergoing long-term treatment with dasatinib to promptly detect and manage potential PE [46].

Mesalazine, commonly used to treat inflammatory bowel diseases like ulcerative colitis and Crohn's disease, contains 5-aminosalicylic acid as its primary active ingredient. This ingredient inhibits intestinal mucosal inflammation by suppressing the synthesis of pro - inflammatory prostaglandins and the formation of inflammatory mediators such as leukotrienes [47, 48]. Despite its proven efficacy, the literature consistently reports rare but severe side effects of Mesalazine, including myocarditis, pericarditis, and PE, with symptoms typically resolving after drug discontinuation [49–51]. However, the exact pathological mechanism of mesalazine-induced PE remains unclear. Existing study indicates that IgE-mediated allergic reactions and direct cardiotoxic effects may be potential pathogenic mechanisms [52]. Specifically, a retrospective study of 52 patients with inflammatory bowel disease revealed that even within the recommended dosage range, most patients may still experience PE due to cardiotoxic reactions to mesalazine, with a median onset time of 14 days [53]. Therefore, clinicians must remain vigilant for this serious complication potentially caused by mesalazine and implement early monitoring and intervention strategies.

In this study, we systematically classified 50 drugs and found that antineoplastic and immunomodulating agents are the most prevalent, followed by cardiovascular and blood system drugs. Notably, a clinical study of 2005 CML patients treated with BCR-ABL1 tyrosine



Drug name	ATC code	PRR(χ2)	EBGM(EBGM05)	IC(IC025)	ROR(95% CI)
Pergolide	N04BC02	34.65 (392.31)	34.63 (21.37)	5.11 (4.3)	35.97(20.2-64.05)
Arsenic Trioxide	L01XX27	27.7 (925.75)	27.65 (20.94)	4.79 (4.31)	28.53(20.47-39.76)
Loncastuximab Tesirine	L01FX22	27.45 (153.04)	27.44 (13.9)	4.78 (3.67)	28.27(12.54-63.71)
Hydralazine	C02DB02	26.85 (2502.27)	26.72 (22.67)	4.74 (3.07)	27.11(22.28-33)
Dinutuximab	L01XC16	22.18 (161.94)	22.18 (12.33)	4.47 (3.5)	22.71(11.26-45.81)
Plerixafor	L03AX16	18.53 (165.89)	18.52 (10.96)	4.21 (3.33)	18.89(10.1-35.33)
Ceritinib	L01XE28	17.13 (713.07)	17.09 (13.42)	4.1 (3.67)	17.44(13.06-23.28)
Denileukin Diftitox	L01XX29	15.59 (41.01)	15.59 (6)	3.96 (2.5)	15.85(5.06-49.62)
Dasatinib	L01XE06	15.53 (4835.6)	15.27 (14)	3.93 (2.27)	15.62(14.07-17.33)
Porfimer	L01XD01	14.48 (62.78)	14.47 (6.91)	3.86 (2.67)	14.69(6.07-35.56)
Rilonacept	L04AC04	13.72 (82.58)	13.71 (7.34)	3.78 (2.75)	13.91(6.59-29.34)
Clofarabine	L01BB06	13.71 (412.13)	13.69 (10.35)	3.77 (3.29)	13.9(9.95-19.42)
Pamidronic Acid	M05BA03	13.35 (661.6)	13.32 (10.72)	3.74 (3.36)	13.54(10.44-17.55)
Abciximab	B01AC13	12.93 (209.23)	12.92 (8.84)	3.69 (3.04)	13.1(8.33-20.61)
Reteplase	B01AD07	12.32 (72.85)	12.31 (6.6)	3.62 (2.59)	12.47(5.92-26.3)
Gadoversetamide	V08CA06	12.3 (51.94)	12.29 (5.87)	3.62 (2.43)	12.45(5.15-30.1)
Pentostatin	L01XX08	12.23 (51.61)	12.23 (5.84)	3.61 (2.42)	12.38(5.12-29.93)
Lorlatinib	L01ED05	11.9 (468.6)	11.87 (9.33)	3.57 (3.15)	12.04(9.03-16.06)
Diazoxide	C02DA01	11.62 (38.85)	11.62 (5.09)	3.54 (2.24)	11.75(4.38-31.52)
Asciminib	L01EA06	10.92 (126.27)	10.92 (7.02)	3.45 (2.7)	11.04(6.52-18.71)
Pyrazinamide	J04AK01	10.25 (33.42)	10.25 (4.49)	3.36 (2.06)	10.36(3.86-27.75)
Anagrelide	L01XX35	9.02 (114.1)	9.01 (5.97)	3.17 (2.47)	9.1(5.56-14.89)
Mesalazine	A07EC02	8.96 (366.97)	8.94 (7.12)	3.16 (1.49)	8.99(6.84-11.8)
Epoprostenol	B01AC09	8.89 (836.21)	8.84 (7.6)	3.14 (2.88)	8.97(7.49-10.74)
Entrectinib	L01EX14	8.79 (82.92)	8.79 (5.46)	3.14 (2.33)	8.87(5.02-15.66)
Penicillamine	M01CC01	8.32 (25.77)	8.32 (3.65)	3.06 (1.76)	8.38(3.13-22.44)
Interferon Alfacon-1	L03AB09	8.29 (32.07)	8.29 (3.97)	3.05 (1.87)	8.35(3.46-20.15)
Bosutinib	L01XE14	8.27 (376.43)	8.25 (6.66)	3.04 (2.67)	8.34(6.45-10.78)
Crizotinib	L01XE16	8.19 (590.86)	8.15 (6.88)	3.03 (2.73)	8.25(6.73-10.11)
Selpercatinib	L01EX22	8 (42.88)	7.99 (4.29)	3 (1.97)	8.06(3.83-16.96)
Gemtuzumab/Ozogamicin	L01FX22	7.91 (108.69)	7.9 (5.36)	2.98 (2.32)	7.97(5.01-12.68)
Bromocriptine	G02CB01	7.65 (52.03)	7.64 (4.41)	2.93 (2.02)	7.7(4-14.85)
Ponatinib	L01XE24	7.51 (410.94)	7.49 (6.17)	2.9 (2.57)	7.56(6.01-9.53)
Cedazuridine/Decitabine	L01BC58	7.49 (44.98)	7.48 (4.18)	2.9 (1.94)	7.54(3.76-15.12)
Tepotinib	L01EX21	7.47 (22.43)	7.47 (3.28)	2.9 (1.6)	7.52(2.81-20.12)
Sirolimus	L04AA10	7.44 (378.31)	7.42 (6.07)	2.89 (2.54)	7.49(5.9-9.52)
Macitentan	C02KX04	7.39 (1613.16)	7.3 (6.63)	2.87 (2.7)	7.44(6.63-8.35)
Covid-19 Vaccine	J07BX03	7.32 (38.23)	7.32 (3.93)	2.87 (1.85)	7.37(3.5-15.51)
Cabergoline	N04BC06	7.3 (130.5)	7.29 (5.21)	2.87 (2.29)	7.35(4.92-10.99)
Busulfan	L01AB01	7.2 (255.92)	7.18 (5.66)	2.84 (2.43)	7.25(5.45-9.63)
Mitoxantrone	L01DB07	7.01 (72.22)	7.01 (4.51)	2.81 (2.06)	7.06(4.17-11.95)
Brigatinib	L01ED04	6.97 (107.47)	6.97 (4.86)	2.8 (2.18)	7.02(4.57-10.79)
Vorinostat	L01XX38	6.58 (47.38)	6.58 (3.91)	2.72 (1.84)	6.62(3.56-12.34)
Gemcitabine	L01BC05	6.5 (840.63)	6.45 (5.71)	2.69 (2.47)	6.54(5.65-7.57)
Daunorubicin	L01DB02	6.44 (36.77)	6.44 (3.6)	2.69 (1.72)	6.48(3.23-12.98)
Decitabine	L01BC08	6.43 (82.5)	6.42 (4.36)	2.68 (2.02)	6.46(4.07-10.28)
Dabigatran etexilate	B01AE07	6.45 (1468.19)	6.36 (5.8)	2.67 (1)	6.46(5.79-7.21)
Dacomitinib	L01EB07	6.24 (17.64)	6.24 (2.74)	2.64 (1.35)	6.28(2.35-16.79)
Gilteritinib	L01EX13	6.18 (73.87)	6.18 (4.14)	2.63 (1.94)	6.22(3.86-10.02)
Pemetrexed	L01BA04	6.13 (350.68)	6.11 (5.09)	2.61 (2.29)	6.16(4.96-7.66)

Fig. 5 Forest plot of the top 50 drugs based on signal strength

kinase inhibitors (TKIs) clearly identified PE as one of the most closely related adverse reactions to TKIs treatment [54]. This may be due to the off-target effects of TKIs on the immune system, specifically their interaction with the PDGFR-β receptor, which could significantly contribute to PE occurrence [55]. Furthermore, in non-small cell lung cancer treatment, a meta-analysis revealed that PD-1 inhibitor monotherapy significantly increases the risk of PE and cardiac tamponade [56]. Multiple studies have further confirmed the association between PD-1 inhibitors and PE [57, 58], yet the exact mechanism remains elusive. It is hypothesized that this may be linked to immunotherapy-induced T-cell overactivation, resulting in myocardial damage and severe complications, including PE and even pericardial tamponade [59]. Cardiovascular drugs, particularly those for pulmonary arterial hypertension, account for a large proportion and warrant our utmost attention regarding safety issues. Specifically, a safety evaluation study of bosentan revealed a correlation between its use and the occurrence of PE [60]. However, the underlying mechanism remains to be further explored. Additionally, direct oral anticoagulants (DOACs) are widely used to prevent embolic events in atrial fibrillation patients, but recent study increasingly suggests an association between DOACs and hemorrhagic PE [15, 61, 62]. Possible reasons for this phenomenon may include drug accumulation due to hepatorenal insufficiency and drug-drug interactions [63].

To explore the temporal patterns of DPE and offer a scientific foundation for optimizing drug administration, we conducted a systematic analysis of the TTO of DPE using the FAERS database. Our findings show that the median TTO for DPE is the shortest with cytarabine, at 14 days, and the longest with digoxin, up to 1624 days. Remarkably, the median TTO for most drugs causing PE is within three months. Additionally, the results of our WSP test indicate that the incidence of DPE decreases over time. This finding suggests that the risk of DPE is highest in the initial treatment stages and progressively

declines thereafter. Consequently, clinicians should closely monitor patients in the early stages of medication.

Among the drugs ranked according to signal strength, pergolide, arsenic trioxide, and loncastuximab tesirine are the top three drugs with the highest signal strength. Pergolide, a dopamine receptor agonist used to treat Parkinson's disease, has been proven to cause valvular tissue fibrosis and thickening by interfering with the metabolism of 5 - hydroxytryptamine and the expression of genes related to its receptors and transporters, ultimately leading to cardiac valve regurgitation [64–66]. Recent studies have shown that the adverse effects of pergolide also extend to the pericardial tissue, promoting its fibrosis and potentially developing into constrictive pericarditis [67]. Both of these conditions can impair the heart's pumping function, leading to congestion in the systemic and pulmonary circulations, elevation of venous pressure, and possible obstruction of pericardial lymphatic return, thus resulting in PE. Arsenic trioxide is commonly used in the treatment of acute promyelocytic leukemia. Multiple studies have shown that patients treated with arsenic trioxide may develop PE or pericarditis [68–70], and the underlying mechanism may be related to the cardiotoxicity induced by arsenic trioxide [71]. Loncastuximab tesirine is a novel antibody-drug conjugate. It is noteworthy that the FDA's drug label has clearly indicated that the use of this drug may cause severe adverse reactions such as effusion and edema. Due to its short marketing time, there is a lack of sufficient clinical evidence. However, in clinical practice, attention still needs to be paid to the potential risk of inducing PE.

This study has several limitations: (1) The spontaneous reporting nature of the FAERS database leads to a proclivity for recording severe events with clear causal relationships, introducing an inherent bias. Concurrently, issues such as data gaps, including the absence of crucial information like patient age, gender, and drug duration, along with under-reporting, have a high likelihood of causing an underestimation or overestimation of risk signals. This, in turn, can impact the accuracy and reliability of conclusions. (2) The majority of reports originate from European and American countries, with limited representation from Asia, which may introduce racial bias. (3) The detected positive signals merely indicate a statistical correlation between drugs and adverse events; clinical trials are necessary to establish their clinical significance. Despite these limitations, our study marks the first exploratory analysis of the FAERS database to identify potential drugs that may induce PE.

Conclusion

In this study, the FAERS database was utilized to identify 26 drugs potentially associated with PE. Notably, 19 of these drugs did not list PE as an ADE in their drug labels. In future research, it is advisable to further integrate electronic health records (EHR) and insurance claim databases to enhance the accuracy and comprehensiveness of the dataset. In addition, logistic regression can be applied to re-evaluate the research findings. Such efforts will enable a deeper understanding of DPE, enhance the precision of drug safety assessment, and provide a more solid basis for decision-making in clinical practice.

Abbreviations

ADE	Adverse drug event
ATC	Anatomical Therapeutic Chemical
CML	Chronic myelogenous leukemia
DOACs	Direct oral anticoagulants
DPE	Drug-induced pericardial effusion
FAERS	The U.S. Food and Drug Administration's Adverse Event Reporting System
HILS	Hydralazine-induced lupus-like syndrome
IQR	Interquartile range
IgE	Immunoglobulin E
PE	Pericardial effusion
PRR	Proportional reporting ratio
PS	Primary suspect
PDGFR-β	Platelet-derived growth factor receptor-β
ROR	Reporting odds ratio
TTO	Time-to-onset
TKIs	Tyrosine kinase inhibitors
WSP	Weibull shape parameter

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions

RGC: Writing – original draft, Writing – review and editing, Software. HPP: Writing – review and editing, Investigation, Validation. DYQ: Conceptualization, Writing – original draft. MXC: Investigation, Supervision, Data curation. All authors reviewed the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

The data for this study was directly obtained from publicly available information in the US Food and Drug Administration Adverse Event Reporting System (FAERS), and therefore does not require ethics committee approval, nor does it involve the issue of participant consent.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Hoit BD. Anatomy and physiology of the Pericardium. Cardiol Clin. 2017;35(4):481–90.
2. McIntyre WF, Jassal DS, Morris AL. Pericardial effusions: do they all require pericardiocentesis? Can J Cardiol. 2015;31(6):812–5.
3. Lazaros G, Lazarou E, Tsioufis P, Soulaidopoulos S, Iliakis P, Vlachopoulos C, et al. Chronic pericardial effusion: current concepts and emerging trends. Expert Rev Cardiovasc Ther. 2022;20(5):363–76.
4. Lazaros G, Vlachopoulos C, Lazarou E, Tsioufis K. New approaches to Management of Pericardial effusions. Curr Cardiol Rep. 2021;23(8):106.
5. Wilson NR, Chauhan S, Aisenberg G. Hydralazine-Induced Lupus Syndrome Manifesting as large Pericardial Effusion. Cureus. 2020;12(8):e9867.
6. Wattal S, Rao MS, Chandra GN, Razak UK, Shetty KR. Dasatinib Induced Cardiac Tamponade-A Rare Association. J Clin Diagn Res. 2017;11(2):FD03–4.
7. Oye M, Oye M, Ali A. Signs of early cardiac tamponade induced by Minoxidil. Am J Emerg Med. 2021;40:e2261–2.
8. Pérez-Casares A, Cesar S, Brunet-Garcia L, Sanchez-de-Toledo J. Echocardiographic evaluation of Pericardial Effusion and Cardiac Tamponade. Front Pediatr. 2017;5:79.
9. Peng L, Xiao K, Ottaviani S, Stebbing J, Wang YJ. A real-world disproportionality analysis of FDA adverse event reporting System (FAERS) events for baricitinib. Expert Opin Drug Saf. 2020;19(11):1505–11.
10. Zhong Y, Li Z, Tao J, Yuan J, Fu Z. Drug-induced myocarditis: a real-world pharmacovigilance study using the FDA adverse event reporting system database. Expert Opin Drug Saf. 2024;17:1–8.
11. Fan M, Niu K, Wu X, Shi H. Risk of drug-induced angioedema: a pharmacovigilance study of FDA adverse event reporting system database. Front Pharmacol. 2024;15:1417596.
12. Li D, Chai S, Wang H, Dong J, Qin C, Du D, et al. Drug-induced QT prolongation and torsade de pointes: a real-world pharmacovigilance study using the FDA adverse event reporting System database. Front Pharmacol. 2023;14:1259611.
13. Das BB, Dodson M, Guzman A. Recurrent pericarditis in an adolescent with Crohn's colitis. Ann Pediatr Cardiol. 2020;13(3):256–9.
14. Kust D, Kruljac I, Peternac AŠ, Ostojić J, Prpić M, Čaržavec D, et al. Pleural and pericardial effusions combined with ascites in a patient with severe sunitinib-induced hypothyroidism. Acta Clin Belg. 2016;71(3):175–7.
15. Shastri P, Bhuta S, Oostra C, Monroe T. Hemopericardium with subsequent cardiac tamponade secondary to rivaroxaban treatment: a case report. Eur Heart J Case Rep. 2020;5(1):ytaa482.
16. Chamsi-Pasha MA, Bassiouny M, Kim ES. Hydralazine-induced lupus syndrome presenting with large pericardial effusion. QJM. 2014;107(4):305–7.
17. Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA adverse event reporting system. Int J Med Sci. 2013;10(7):796–803.
18. Bate A. Bayesian confidence propagation neural network. Drug Saf. 2007;30(7):623–5.
19. Heo SJ, Jung I. Extended multi-item gamma Poisson shrinker methods based on the zero-inflated Poisson model for postmarket drug safety surveillance. Stat Med. 2020;39(30):4636–50.
20. Chen XD, Xiao KH, Zhou CB. Drug-induced retinal vein occlusion: a disproportionality analysis from the FDA adverse event reporting system (2004–2023). Front Pharmacol. 2024;15:1480269.
21. Sauzet O, Carvajal A, Escudero A, Molokhia M, Cornelius VR. Illustration of the weibull shape parameter signal detection tool using electronic healthcare record data. Drug Saf. 2013;36(10):995–1006.
22. Gong J, Drobni ZD, Zafar A, Quinaglia T, Hartmann S, Gilman HK, et al. Pericardial disease in patients treated with immune checkpoint inhibitors. J Immunother Cancer. 2021;9(6):e002771.
23. Kaushik VV. Review of Biosimilars of Adalimumab. J Assoc Physicians India. 2017;65:15–21.
24. Lee S, Lafian A, Mahani T, Hojjati M. Adalimumab-Induced Lupus Serositis: a Case Report and Review of the literature. Cureus. 2023;15(2):e34568.
25. Kelly D, O'Connell O, Henry M. Adalimumab-induced lupus serositis. BMJ Case Rep. 2015;2015:bcr2014207323.
26. Ozkan H, Cetinkaya AS, Yildiz T, Bozat T. A rare side effect due to TNF-Alpha blocking Agent: Acute Pleuropericarditis with Adalimumab. Case Rep Rheumatol. 2013;2013:985914.
27. Paydas S. Management of adverse effects/toxicity of ibrutinib. Crit Rev Oncol Hematol. 2019;136:56–63.
28. Johnson G, Baviriseaty N, Massanet N, Kooper J. Serositis causing pericardial and pleural effusions after eight years of maintenance ibrutinib for Waldenstrom's macroglobulinemia. J Oncol Pharm Pract. 2023;25:10781552231171925.
29. Fakhri B, Wang V, Perez-Burbano G, Wall A, Mandrekar S, Parikh SA, Woyach J, Shanafelt T. Pericardial events associated with ibrutinib-based therapies for chronic lymphocytic leukaemia in two landmark trials. Br J Haematol. 2024;205(4):1645–8.
30. Zhai Y, Hu F, Shi W, Ye X, Xu J, Guo X, et al. Pharmacovigilance analysis of cardiac risks associated with Bruton tyrosine kinase inhibitors. Expert Opin Drug Saf. 2023;22(9):857–69.
31. Miatech JL, Hughes JH, McCarty DK, Stagg MP. Ibrutinib-Associated Cardiac Tamponade with Concurrent Antiplatelet Therapy. Case Rep Hematol. 2020;2020:4282486.
32. Jeelani H, Sheikh MM, Tahir N, Ying G, Prasad S, Yaremko M, et al. Left atrial appendage occlusion as an alternative to anticoagulants in Ibrutinib-Induced Hemorrhagic Pericardial Effusion. JACC Case Rep. 2022;4(12):751–4.
33. Aslan Candır B, Yiğenoğlu TN, Kızıl Çakar M, Dal MS, Altuntaş F. Non hemorrhagic pericardial effusion from ibrutinib in a patient without comorbidities. J Oncol Pharm Pract. 2022;28(4):972–4.
34. Li W, Liu C, Zhang Z, Cai Z, Lv T, Zhang R, et al. Exploring the top 30 drugs associated with drug-induced constipation based on the FDA adverse event reporting system. Front Pharmacol. 2024;15:1443555.
35. Shahzad Qamar A, Zamir A, Khalid S, Ashraf W, Imran I, Hussain I, et al. A review on the clinical pharmacokinetics of hydralazine. Expert Opin Drug Metab Toxicol. 2022;18(10):707–14.
36. Elkholy KO, Akhtar H, Chakraborti A. A case of Seronegative ANA Hydralazine-Induced Lupus presenting with Pericardial Effusion and Pleural Effusion. Cureus. 2020;12(8):e9831.
37. Zeitjian V, Mehdizadeh A. ANA-Negative Hydralazine-Induced Pericardial Effusion. Case Rep Med. 2017;2017:3521541.
38. Rahman MF, Panezai MA, Szerlip HM. Hydralazine-induced pericardial effusion. Proc (Bayl Univ Med Cent). 2019;32(3):377–8.
39. He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. Curr Opin Rheumatol. 2018;30(5):490–7.
40. Iyer P, Dirweesh A, Zijoo R. Hydralazine Induced Lupus Syndrome presenting with recurrent Pericardial Effusion and a negative antinuclear antibody. Case Rep Rheumatol. 2017;2017:5245904.
41. Solomon-Tsegaye T, Treadwell EL, Obi R, Pitzalis M. Antinuclear antibody-negative lupus? An ominous presentation of hydralazine-induced lupus syndrome. Eur J Rheumatol. 2018;5(4):272–4.
42. Hořínková J, Šíma M, Slanař O. Pharmacokinetics of Dasatinib. Prague Med Rep. 2019;120(2–3):52–63.
43. Levêque D, Becker G, Bilger K, Natarajan-Amé S. Clinical pharmacokinetics and pharmacodynamics of Dasatinib. Clin Pharmacokinet. 2020;59(7):849–56.
44. Shin H, Ha JE, Zang DY, Kim SH, Do YR, Lee WS, et al. Appropriate starting dose of Dasatinib based on analyses of dose-limiting toxicities and molecular responses in Asian patients with chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk. 2021;21(6):e521–9.
45. Zhao W, Wang K, Yu L, Guo Y, Li Z. Dasatinib-induced pleural effusions, pericardial effusion and pulmonary arterial hypertension: a case report. Transl Pediatr. 2024;13(4):673–81.
46. Krauth MT, Herndlhofer S, Schmook MT, Mitterbauer-Hohendanner G, Schlögl E, Valent P. Extensive pleural and pericardial effusion in chronic myeloid leukemia during treatment with dasatinib at 100 mg or 50 mg daily. Haematologica. 2011;96(1):163–6.
47. Veloso PM, Machado R, Nobre C. Mesalazine and inflammatory bowel disease - from well-established therapies to progress beyond the state of the art. Eur J Pharm Biopharm. 2021;167:89–103.
48. Criscuoli V, Modesto I, Orlando A, Cottone M. Mesalazine for the treatment of inflammatory bowel disease. Expert Opin Pharmacother. 2013;14(12):1669–78.
49. Vayre F, Vayre-Oundjian L, Monsuez JJ. Pericarditis associated with longstanding mesalazine administration in a patient. Int J Cardiol. 1999;68(2):243–5.
50. Radhakrishnan ST, Mohanaruban A, Hoque S. Mesalazine-induced myocarditis: a case report. J Med Case Rep. 2018;12(1):44.

51. Ezquerra A, Resina E, Montes Á, Álvarez-Malé T, Gisbert P. Pericardial effusion associated with mesalamine treatment in a patient with ulcerative colitis. Gastroenterol Hepatol. 2021;44(10):721–3.
52. Sonu I, Wong R, Rothenberg ME. 5-ASA induced recurrent myopericarditis and cardiac tamponade in a patient with ulcerative colitis. Dig Dis Sci. 2013;58(8):2148–50.
53. Chen J, Duan T, Fang W, Liu S, Wang C. Analysis of clinical characteristics of mesalazine-induced cardiotoxicity. Front Pharmacol. 2022;13:970597.
54. Lin J, Makenbaeva D, Lingohr-Smith M, Bilmes R. Healthcare and economic burden of adverse events among patients with chronic myelogenous leukemia treated with BCR-ABL1 tyrosine kinase inhibitors. J Med Econ. 2017;20(7):687–91.
55. Agrawal V, Christenson ES, Showel MM. Tyrosine kinase inhibitor induced isolated pericardial effusion. Case Rep Oncol. 2015;8(1):88–93.
56. Li H, Han D, Zhang L, Feng X, Li H, Yang F, et al. PD-1/L1 inhibitors may increase the risk of pericardial disease in non-small-cell lung cancer patients: a meta-analysis and systematic review. Immunotherapy. 2022;14(7):577–92.
57. Saade A, Mansuet-Lupo A, Arrondeau J, Thibault C, Mirabel M, Goldwasser F, Oudard S, Weiss L. Pericardial effusion under nivolumab: case-reports and review of the literature. J Immunother Cancer. 2019;7(1):266.
58. Tachihara M, Yamamoto M, Yumura M, Yoshizaki A, Kobayashi K, Nishimura Y. Non-parallel anti-tumour effects of pembrolizumab: a case of cardial tamponade. Respirol Case Rep. 2019;7(3):e00404.
59. Tang M, Dang P, Liu T, Yang K, Wang Y, Tse G, et al. Risk factors and outcomes of pericardial effusion in cancer patients receiving PD-1 inhibitors. Int J Cardiol. 2024;407:132029.
60. Hamaguchi Y, Sumida T, Kawaguchi Y, Ihn H, Tanaka S, Asano Y, et al. Safety and tolerability of bosentan for digital ulcers in Japanese patients with systemic sclerosis: prospective, multicenter, open-label study. J Dermatol. 2017;44(1):13–7.
61. Nasir SA, Babu Pokhrel N, Baig A. Hemorrhagic Pericardial Effusion from Apixaban Use: Case Report and Literature Review. Cureus. 2022;14(10):e30021.
62. Cinelli M, Uddin A, Duka I, Soomro A, Tamburrino F, Ghavami F, et al. Spontaneous hemorrhagic Pericardial and Pleural Effusion in a patient receiving apixaban. Cardiol Res. 2019;10(4):249–52.
63. Latif R, Aloqaily M, Rabadi A, Arshad K, Kurian AI, Obeidat I, et al. Apixaban-Induced Hemopericardium in a Post-TAVR patient: a Case Report highlighting Diagnostic and Management challenges. Am J Case Rep. 2024;25:e944173.
64. Andrejak M, Tribouilloy C. Drug-induced valvular heart disease: an update. Arch Cardiovasc Dis. 2013;106(5):333–9.
65. Bhattacharyya S, Schapira AH, Mikhailidis DP, Davar J. Drug-induced fibrotic valvular heart disease. Lancet. 2009;374(9689):577–85.
66. Oury C, Maréchal P, Donis N, Hulin A, Hego A, Tridetti J, et al. Dexfenfluramine and Pergolide cause Heart Valve Disease via Valve metabolic reprogramming and Ongoing Matrix Remodeling. Int J Mol Sci. 2020;21(11):4003.
67. Andreatta W, Shah P. Reversible hypotony and Choroidal Effusion following the Use of Pergolide for Parkinson's Disease. Semin Ophthalmol. 2015;30(5–6):423–5.
68. Khizer U, Annam B, Akhtar A, Dhaliwal JS, Yang C. Fatal differentiation syndrome complicating Acute promyelocytic leukemia treatment: a Case Report. Cureus. 2024;16(2):e54491.
69. Atar M, Majid M, Yaker Z, Agrawal A, Arockiam AD, Gerds AT, et al. Successful treatment of recurrent Pericarditis with Rilonacept in Acute promyelocytic leukemia. JACC Case Rep. 2023;25:102043.
70. Ueda K, Nagai S, Miyashita SI, Kaise T, Ichikawa M, Kumano K, et al. Arsenic-induced pericardial and pleural effusion without acute promyelocytic leukemia differentiation syndrome. Leuk Res. 2010;34(1):e25–6.
71. Vineetha VP, Raghu KG. An overview on Arsenic Trioxide-Induced Cardiotoxicity. Cardiovasc Toxicol. 2019r;19(2):105–19.

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