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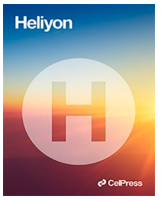

Research article

Sorafenib safety evaluation: Real-world analysis of adverse events from the FAERS database

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ABSTRACT

Background: Sorafenib is approved for the targeted therapy of cancers such as liver cancer and renal cancer. Given its widespread use, drug-related adverse events have received attention, and the post-marketing regulatory link is crucial.
Objective: By using the FAERS database to mine the adverse events (AEs) related to sorafenib, comparing the association intensity of key AEs, and exploring potential drug-related AEs, it provides a reference for clinical medication.
Methods: Collect ADE data related to sorafenib in the FAERS database from 2006 to 2023. Standardize the data, and map adverse events to system organ classes and preferred terms. Analyze using various signal quantification techniques such as ROR, PRR, BCPNN, and MGPS.
Results: Among 18,520 adverse event reports (AERs) where sorafenib was the primary suspected drug, a total of 390 preferred terms (PTs) of adverse reactions were identified, covering 24 different system organ classes (SOCs). Specifically, the adverse events of sorafenib mainly involve the digestive system, skin and subcutaneous tissue, as well as non-specific physical discomfort including infection and injury. Among them, digestive system symptoms and skin toxicity are typical adverse reactions of sorafenib. We also observed uncommon but clearly strong AE signals, such as chloracne (n = 3, ROR 1756.39, PRR 1756.32, IC 8.78, EBGM 439.83), low-differentiated thyroid cancer (n = 4, ROR 585.47, PRR 585.44, IC 8.2, EBGM 293.22). It is worth noting that palmar-plantar erythrodysaesthesia syndrome (n = 2109, ROR 73.98, PRR 72.03, IC 6.01, EBGM 64.25) and hepatic encephalopathy (n = 457, ROR 37.44, PRR 37.23, IC 5.13, EBGM 35.07) have a higher incidence and signal intensity. In addition, we also observed some adverse events not mentioned in the official drug instructions, such as vitamin K deficiency or increased protein induced by antagonist II (PIVKA-II), abnormal alpha-fetoprotein, tumor metastasis, and splenic atrophy.
Conclusion: Sorafenib carries the risk of various adverse reactions while providing therapeutic effects. In clinical applications, physicians should closely monitor the occurrence of digestive system reactions, skin lesions, endocrine system lesions, as well as injuries, infections, and other events.

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1. Introduction

With the aging of the population and changes in lifestyles, the global incidence of tumors is on the rise [1]. Various types of cancers, including lung cancer, breast cancer, prostate cancer, and colorectal cancer, are increasing to varying degrees [2,3]. According to data released by the World Health Organization (WHO), the global incidence of tumors has surged by approximately 20 % over the past decade [4]. Tumors have also become one of the leading causes of death worldwide, posing a significant public health challenge [5].

The in-depth study of tumor biology and molecular mechanisms has led to the discovery, development, and clinical application of targeted antitumor drugs, particularly tyrosine kinase inhibitors (TKIs) [6,7]. TKIs are specifically designed to inhibit cancer growth, metastasis, and survival, offering more personalized and effective treatment options for patients [8,9]. Many of these targeted drugs have become standard treatments for various cancer types [10,11]. However, TKIs are a double-edged sword, as their clinical application often comes with notable side effects and adverse events [12].

Sorafenib plays a pivotal role in the field of TKIs. It is primarily used to treat cancers such as renal cancer and liver cancer [13]. Sorafenib's mechanism of action involves inhibiting multiple kinases within tumor cells, such as the vascular endothelial growth factor receptor (VEGFR) and Raf kinase, thereby blocking tumor angiogenesis and cell proliferation. This inhibition helps to slow tumor growth and spread, ultimately improving patient survival rates [14,15]. As one of the first targeted drugs approved for renal and liver cancer, sorafenib has marked a significant breakthrough in treating these diseases. Compared to traditional chemotherapy, sorafenib offers better therapeutic outcomes with relatively fewer adverse effects [16,17].

In recent years, the advent of immunotherapy (IO), particularly immune checkpoint inhibitors, has significantly altered the landscape of cancer treatment, especially for hepatocellular carcinoma (HCC) [18,19]. IO has revolutionized HCC treatment by enhancing the immune system's ability to combat cancer. This shift has led to the increasing use of combinatorial strategies, integrating IO with treatments such as transarterial chemoembolization (TACE) and locoregional therapies. These combinations have shown promise in improving patient outcomes and are becoming central to HCC management [20]. Additionally, the combination of targeted therapy and immunotherapy has opened new treatment avenues for many cancer patients who are not candidates for surgery. The scope of sorafenib's application, as a key targeted therapy, is also gradually expanding. However, sorafenib remains crucial in specific clinical scenarios, particularly where IO is contraindicated or unavailable, and continues to be an active area of research [21].

As sorafenib becomes more widely used, the attention to its associated adverse reactions and drug-related adverse events, such as hand-foot syndrome, hypertension, and diarrhea, has also increased [22,23]. Monitoring these adverse events is essential to ensure patient safety and optimize treatment outcomes. It facilitates personalized treatment plans, assists healthcare providers in drug management, and supports the development of monitoring and preventive measures. These efforts ultimately contribute to optimizing treatment protocols, improving patients' quality of life, and advancing the medical field.

The FAERS database, managed by the U.S. Food and Drug Administration (FDA), is a platform for collecting and analyzing adverse drug events (ADEs) related to drug use [24]. It gathers information on adverse events linked to drugs, biological products, and medical devices, reported by healthcare professionals, patients, and drug manufacturers [25,26]. This database includes detailed information such as descriptions of adverse events, patient demographics, and medication usage [27]. Analyzing the FAERS database allows us to identify safety concerns related to drugs in real-world use, including rare adverse reactions and drug interactions. This is highly

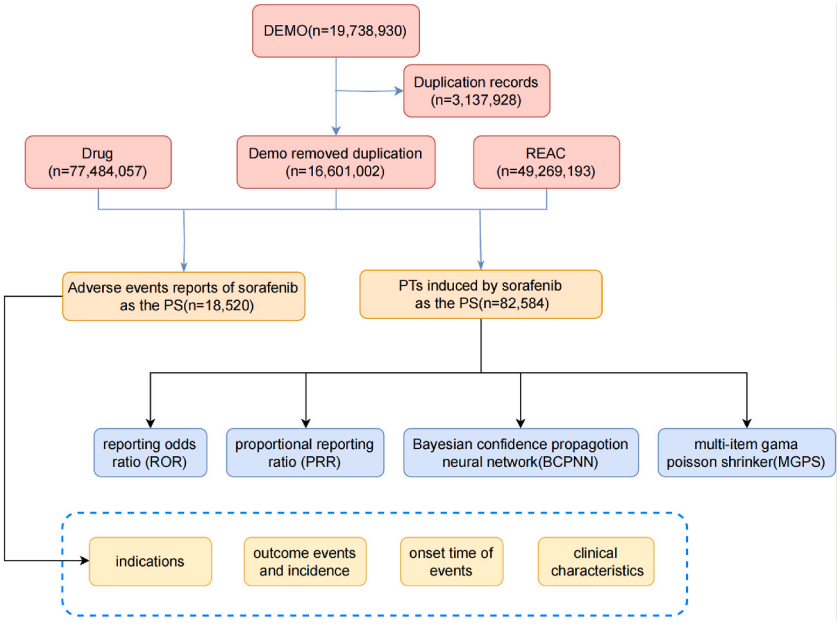

Fig. 1. The flow diagram of selecting sorafenib-related AEs from FAERS database.

valuable for drug research, regulation, and clinical practice.

In this study, we conducted a comprehensive evaluation of the safety profile of sorafenib in real-world use by analyzing adverse events (AEs) reported in the FAERS database. Through data mining of FAERS, we aimed to identify potential safety issues related to sorafenib, providing valuable reference information for clinical use. Additionally, by analyzing the occurrence of AEs across different patient populations (e.g., age, gender, disease status), we sought to identify potential high-risk groups. This would equip clinicians with more detailed safety information when prescribing sorafenib, aiding them in making informed clinical decisions.

2. Methods

2.1. Data source

This retrospective, observational disproportionality analysis was conducted using data from the FAERS database to evaluate the safety profile of sorafenib, with a particular focus on its association with various AEs. FAERS is a global spontaneous reporting database that aggregates post-marketing safety data on approved drugs, providing an essential resource for pharmacovigilance activities such as safety signal detection and the quantification of drug-AE relationships. Reports to FAERS are submitted by drug manufacturers, healthcare professionals, and consumers, ensuring a broad spectrum of data sources.

Given that sorafenib was approved by the FDA in 2005, this study included all relevant reports from the first quarter of 2006 through to the most recent available data from Q3 2023. The data was obtained from the publicly accessible FAERS Quarterly Data Extract Files (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm). The analysis encompassed seven FAERS data categories, including patient demographics, drug information, adverse events, outcomes, report sources, and indications. By systematically analyzing these categories, this study aimed to identify and quantify the disproportionality between sorafenib and the adverse events of interest.

A comprehensive flow diagram, presented as Fig. 1, illustrates the key steps in the data extraction process from the FAERS database files. This includes data preprocessing and deduplication, the classification of adverse events using the MedDRA terminology, the summarization of clinical characteristics, and the subsequent disproportionality analysis to detect safety signals related to sorafenib.

2.2. Data extraction and processing

In our analysis, the involvement of sorafenib in adverse events was categorized into four classifications: primary suspect, secondary suspect, concomitant, or interacting. For this study, we focused primarily on reports where sorafenib was designated as the primary suspect drug. Adverse events were coded using the Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA) and were then mapped to System Organ Classes (SOCs) to facilitate a systematic classification and analysis of the data [28].

We eliminated duplicate reports. The most recent report based on the date was retained for data with the same caseid in the DEMO table. By using the primaryid field, the relationships between data sets were established. The drug names were standardized through the Medex_UIMA_1.8.3 system. Reports that suspected sorafenib as the primary drug associated with ADEs were extracted [29]. These reports covered various pieces of information, such as the reporting date, the patient's age and gender, the reporter, and the region.

2.3. Data statistics and analysis

In this study, four algorithms, namely reporting odds ratios (ROR) [30], proportional reporting ratios (PRR) [31], Bayesian Confidence Propagation Neural Network (BCPNN) [32], and Multi-item Gamma-Poisson Shrinker (MGPS) [33], were simultaneously applied to detect drug ADE signals.

This study combines the use of ROR, PRR, BCPNN, and MGPS algorithms to give full play to their respective strengths, expand the detection range, verify the results from multiple perspectives, make effective use of the characteristics of different algorithms, and detect more comprehensive and reliable safety signals. The advantage of ROR is that it can correct the bias caused by the small number of reports of some events. In contrast, the advantage of PRR is its higher specificity. BCPNN performs well in integrating multi-source data and cross-validation. The strength of MGPS is its ability to detect signals from rare events. The combined use of multiple algorithms allows for cross-validation, reducing false positives, and by adjusting the threshold and variance, more potential rare adverse reactions can be detected.

All algorithms are based on 2 x 2 contingency tables (as presented in Table 1). For specific formulas and threshold values, please refer to Table 2. Statistical analysis was performed using the R program (version 4.2.1). A higher value indicates a stronger signal intensity, suggesting a stronger association between the target drug and adverse events.

Table 1
Four grid table.

	Sorafenib-related ADEs	Non- Sorafenib -related ADEs	Total
Sorafenib	a	b	a+b
Non- Sorafenib	c	d	c+d
Total	a+c	b+d	N=a+b+c+d

Table 2
ROR, PRR, BCPNN, and EBGM methods, formulas, and thresholds.

Method	Formula	Threshold
ROR	$ROR = \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$	a ≥3 and 95 % CI (lower limit)
	$SE(lnROR) = \sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}$	>1
	$95\%CI = e^{ln(ROR)\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$	
PRR	$PRR = \frac{a/(a+b)}{c/(c+d)}$	a ≥3 and 95 % CI (lower limit)
	$SE(lnPRR) = \sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}$	>1
	$95\%CI = e^{ln(PRR)\pm 1.96\sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}}$	
BCPNN	$IC = log_2\frac{p(x,y)}{p(x)p(y)} = log_2\frac{a(a+b+c+d)}{(a+b)(a+c)}$	IC025 > 0
	$E(IC) = log_2\frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$	
	$V(IC) = \frac{1}{(ln\,2)^2}\left\{\left[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}\right]+\left[\frac{(a+b+c+d)-(a+b)+\alpha-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}\right]+\left[\frac{(a+b+c+d)-(a+c)+\beta-\beta 1}{(a+c+\beta 1)(1+a+b+c+d+\beta)}\right]\right\}$	
	$\gamma = \gamma 11\frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$	
	$IC-2SD = E(IC)-2\sqrt{V(IC)}$	
EBGM	$EBGM = \frac{a(a+b+c+d)}{(a+c)(a+b)}$	EBGM05 > 2
	$95\%CI = e^{ln(EBGM)\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$	

3. Results

3.1. Basic information about adverse events of sorafenib

From the first quarter of 2006 to the third quarter of 2023, a total of 49,269,193 adverse events (AEs) from the FAERS database were collected in this study, of which 82,584 were sorafenib identified as the primary suspected drug of adverse drug events (ADEs), and these AEs involved 18,520 adverse event reports (AERs).

In the reports of AEs involving sorafenib, the number of male patients (66.94 %) was significantly higher than that of female patients (26.25 %). Regarding age, some data (19.43 %) did not provide age information. In the reports with clear age data, the age group of 60–80 years old was the most common (48.22 %). In terms of reporters, the majority (41.20 %) of the reports came from physicians, followed by consumers (21.13 %) and other health-professionals (17.90 %). Among the reported countries that have been counted, the majority of reports came from the United States (19.97 %) and Japan (10.94 %). In terms of clinical outcomes, except for undefined serious adverse events, AEs that led to hospitalization were the most common (32.36 %), followed by death (20.24 %). From the perspective of the time of occurrence of AEs, in the clear data, the proportion of AEs occurring within <7 days of medication (17.78 %) and 7–28 days of medication (18.62 %) was the highest. For more details, see Table 3.

3.2. System organ class of adverse event reports

This study found that the adverse reactions of sorafenib involved 24 system organ classes (SOCs) by analyzing the AERs of sorafenib, as depicted in Fig. 2. The three most common systems are Gastrointestinal disorders (n = 12553, ROR 1.93, PRR 1.78, IC 0.83, EBGM 1.78), General disorders and administration site conditions (n = 10787, ROR 0.71, PRR 0.75, IC -0.42, EBGM 0.75), and Skin and subcutaneous tissue disorders (n = 10358, ROR 2.54, PRR 2.34, IC 1.22, EBGM 2.33). General disorders and administration site conditions refer to some non-specific physical discomfort or problems associated with the use of medications, which may include symptoms such as fatigue, pain, and fever. This is in line with the characteristics of sorafenib as a tumor-targeted therapeutic drug. See Table 4 for details.

3.3. Signal of preferred terms

At the preferred term (PT) level, our study used four algorithms to analyze AERs, and evaluate their compliance with various screening criteria, resulting in 390 PTs, as shown in Supplementary Material 1. The waterfall chart of the signal intensity of all AE at the PT level is shown in Fig. 3. Based on the ranking based on the EBGM algorithm, we listed the top 30 PTs with high signal intensity in

Table 3
Basic information on ADEs related to Sorafenib from the FAERS database.

Variable	Number of events (%)
Gender	
female	4861(26.25)
male	12398(66.94)
unkown	1261(6.81)
Age	
<18	200(1.08)
18~40	548(2.96)
40~60	4023(21.72)
60~80	8930(48.22)
≥80	1221(6.59)
unknow	3598(19.43)
Reporter	
Physician	7631(41.20)
Consumer	3913(21.13)
Other health-professional	3315(17.90)
Pharmacist	2142(11.57)
unkown	1514(8.17)
Registered Nurse	5(0.03)
Reported countries (Top 5)	
other	10680(57.67)
United States	3699(19.97)
Japan	1943(10.49)
China	646(3.49)
Brazil	457(2.47)
Outcomes (Top 5)	
other serious	9312(41.38)
hospitalization	7283(32.36)
death	4556(20.24)
life threatening	912(4.05)
disability	425(1.89)
Adverse event occurrence time - medication date (days)	
<7	2647(17.78)
7~28	2772(18.62)
28~56	1300(8.73)
≥56	2604(17.49)
unknow	5563(37.37)
Year of report	
2006	990(5.35)
2007	819(4.42)
2008	821(4.43)
2009	1158(6.25)
2010	1487(8.03)
2011	1652(8.92)
2012	1367(7.38)
2013	1008(5.44)
2014	1158(6.25)
2015	1304(7.04)
2016	1005(5.43)
2017	1318(7.12)
2018	1420(7.67)
2019	954(5.15)
2020	709(3.83)
2021	565(3.05)
2022	429(2.32)
2023	356(1.92)

Table 5. Among them, significant signal intensities were observed in chloracne (n = 3, ROR 1756.39, PRR 1756.32, IC 8.78, EBGM 439.83), poorly differentiated thyroid carcinoma (n = 4, ROR 585.47, PRR 585.44, IC 8.2, EBGM 293.22), protein induced by vitamin K absence or antagonist II increased (n = 17, ROR 321.12, PRR 321.05, IC 7.7, EBGM 207.7), and alpha 1 foetoprotein increased (n = 142, ROR 192.34, PRR 191.99, IC 7.18, EBGM 144.83), etc., which may be related to the action of sorafenib on the human immune system and metabolic processes, in line with the characteristics of sorafenib as a targeted therapy drug for tumors. In addition, palmar-plantar erythrodysaesthesia syndrome (n = 2109, ROR 73.98, PRR 72.03, IC 6.01, EBGM 64.25) showed significant intensity, accompanied by a large number of case reports, which is consistent with the instruction manual indicating that hand and foot skin reactions may occur after medication.

We also observed that some adverse reactions in the digestive system, such as food refusal and spleen atrophy, and some skin adverse reactions, such as plantar erythema, palmoplantar keratoderma, and hyperkeratosis, all showed strong signals, which is

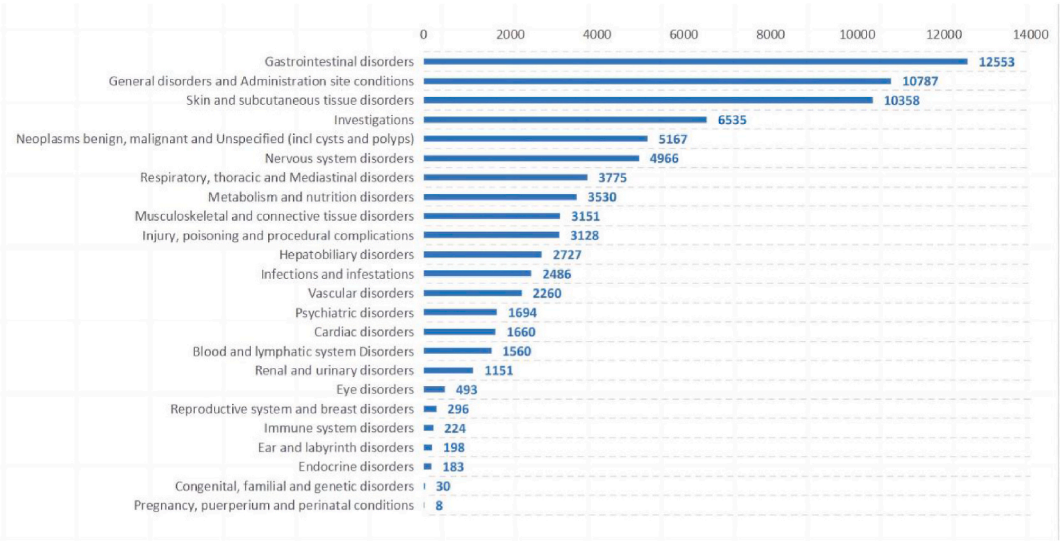

Fig. 2. The number of AERs related to Sorafenib at the SOC level in FAERS database.

consistent with the common adverse events related to sorafenib that we observed in the clinic. The details are listed in Table 5.

4. Discussion

Sorafenib, a tyrosine kinase inhibitor (TKI) introduced in December 2005, is a targeted anti-tumor agent primarily used in the treatment of liver, kidney, and thyroid cancers. By inhibiting key signal transduction pathways in tumor cells, it effectively suppresses tumor growth, proliferation, and metastasis. Pharmacological studies have identified its primary molecular targets within tumor cells, including CRAF, BRAF, V600E BRAF, c-Kit, and FLT-3, as well as vascular targets such as CRAF, VEGFR-2, VEGFR-3, and PDGFR-β [34,35]. In a randomized, double-blind phase 3 trial for thyroid cancer, patients treated with sorafenib showed a significantly longer median progression-free survival (10.8 months) compared to those in the placebo group (5.8 months; hazard ratio 0.59, 95 % CI 0.45–0.76; $p < 0.0001$). Notably, improvements were observed across all pre-specified clinical and genetic biomarker subgroups. However, 98.6 % of patients in the sorafenib group experienced adverse events, with the most common being hand-foot skin reactions (76.3 %), diarrhea (68.6 %), alopecia (67.1 %), and rash or desquamation (50.2 %) [22]. In another study conducted from 2013 to 2015 involving 476 patients with unresectable hepatocellular carcinoma (HCC) treated with sorafenib as a first-line therapy, the median survival time was reported as 12.3 months. The most frequently observed adverse events included palmar-plantar erythrodysaesthesia (52 %), diarrhea (46 %), hypertension (30 %), and decreased appetite (27 %) [36]. A phase III randomized, double-blind, placebo-controlled trial focusing on advanced HCC patients in the Asia-Pacific region also demonstrated that patients receiving sorafenib had a significantly better median overall survival (6.5 months) compared to the placebo group (4.2 months), with commonly reported drug-related adverse events being hand-foot skin reactions, diarrhea, and fatigue. Notably, these adverse events rarely led to drug discontinuation, and patients generally tolerated the treatment well [37]. Some studies have indicated that combining sorafenib with immunotherapy could enhance its safety and effectiveness in treating advanced tumors, positioning it as a potential first-line treatment option [38]. However, other studies have compared sorafenib to newer targeted therapies, suggesting that its efficacy and safety may not be superior, and highlighting the need for larger, more comprehensive trials [39].

The above studies show that sorafenib has significant therapeutic effects and potential safety advantages in the targeted treatment of tumors. This study systematically evaluated the adverse reactions related to sorafenib by in-depth analysis of the FAERS database from the first quarter of 2006 to the third quarter of 2023. In this process, this study not only confirmed some existing safety information, but also revealed new potential risks. This provides more comprehensive and accurate data support for medical practice and medication decisions.

This study observed that the proportion of male patients in the reports of adverse events of sorafenib was significantly higher than that of female patients. This may be related to the fact that both hepatocellular carcinoma and renal cell carcinoma are more common in men. At the age level, the highest proportion of adverse event reports was in patients aged 60–80. The analysis of the reasons may be: firstly, tumors are more common in the elderly, so there are more elderly patients taking sorafenib. Secondly, the metabolic capacity of the liver and kidneys of elderly patients decreases, which will affect the metabolism and clearance of the drug, increasing the risk of adverse reactions. Finally, the elderly are often likely to suffer from multiple diseases at the same time and need to take multiple medications, and the interaction between medications may increase the probability of adverse reactions. In terms of reporters, most of the adverse reaction reports are submitted by medical professionals, which shows that doctors are more likely to discover and report adverse reactions by closely observing the symptoms and signs of patients during the treatment process. Regarding the time of adverse events, most of them are concentrated in the range of 7–28 days after taking the medication. According to pharmacokinetics, the blood

Table 4
The signal strength of AERs of Sorafenib at the SOC level in FAERS database.

System organ class (SOC)	Case Reports	ROR(95 % CI)	PRR(95 % CI)	χ^2	IC(IC025)	EBGM (EBGM05)
Gastrointestinal disorders	12553	1.93(1.89, 1.96)	1.78(1.75, 1.82)	4680.38	0.83(0.8)	1.78(1.75)
General disorders and administration site conditions	10787	0.71(0.69, 0.72)	0.75(0.74, 0.76)	1113.17	−0.42 (-0.45)	0.75(0.74)
Skin and subcutaneous tissue disorders	10358	2.54(2.49, 2.59)	2.34(2.29, 2.39)	8376.44	1.22(1.19)	2.33(2.29)
Investigations	6535	1.32(1.29, 1.36)	1.3(1.27, 1.33)	474.81	0.37(0.34)	1.3(1.27)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5167	2.37(2.3, 2.44)	2.28(2.24, 2.33)	3807.57	1.19(1.15)	2.27(2.22)
Nervous system disorders	4966	0.69(0.67, 0.71)	0.71(0.7, 0.72)	664.49	−0.5(-0.54)	0.71(0.69)
Respiratory, thoracic and mediastinal disorders	3775	0.96(0.93, 0.99)	0.96(0.92, 1)	6.37	−0.06(-0.1)	0.96(0.93)
Metabolism and nutrition disorders	3530	2.04(1.97, 2.11)	1.99(1.91, 2.07)	1776.98	0.99(0.94)	1.99(1.93)
Musculoskeletal and connective tissue disorders	3151	0.7(0.68, 0.73)	0.72(0.69, 0.75)	378.29	−0.48 (-0.53)	0.72(0.69)
Injury, poisoning and procedural complications	3128	0.4(0.38, 0.41)	0.42(0.4, 0.44)	2773.33	−1.25(-1.3)	0.42(0.41)
Hepatobiliary disorders	2727	3.8(3.66, 3.95)	3.7(3.56, 3.85)	5402.25	1.88(1.83)	3.69(3.57)
Infections and infestations	2486	0.56(0.54, 0.59)	0.58(0.56, 0.6)	819.21	−0.79 (-0.85)	0.58(0.56)
Vascular disorders	2260	1.27(1.22, 1.33)	1.26(1.21, 1.31)	127.05	0.34(0.28)	1.26(1.22)
Psychiatric disorders	1694	0.34(0.33, 0.36)	0.36(0.35, 0.37)	2078.08	−1.48 (-1.55)	0.36(0.34)
Cardiac disorders	1660	0.75(0.72, 0.79)	0.76(0.73, 0.79)	129.54	−0.4(-0.47)	0.76(0.73)
Blood and lymphatic system disorders	1560	1.13(1.08, 1.19)	1.13(1.07, 1.2)	23.33	0.17(0.1)	1.13(1.08)
Renal and urinary disorders	1151	0.74(0.7, 0.79)	0.75(0.71, 0.8)	101.01	−0.42 (-0.51)	0.75(0.71)
Eye disorders	493	0.29(0.27, 0.32)	0.3(0.28, 0.32)	828.25	−1.74 (-1.87)	0.3(0.28)
Reproductive system and breast disorders	296	0.42(0.38, 0.48)	0.43(0.38, 0.48)	230.49	−1.23 (-1.39)	0.43(0.39)
Immune system disorders	224	0.24(0.21, 0.28)	0.24(0.21, 0.28)	528.26	−2.03 (-2.22)	0.24(0.22)
Ear and labyrinth disorders	198	0.55(0.48, 0.64)	0.56(0.49, 0.64)	70.5	−0.85 (-1.05)	0.56(0.5)
Endocrine disorders	183	0.89(0.77, 1.03)	0.89(0.78, 1.02)	2.44	−0.17 (-0.37)	0.89(0.79)
Congenital, familial and genetic disorders	30	0.12(0.08, 0.17)	0.12(0.08, 0.17)	202.13	−3.1(-3.61)	0.12(0.09)
Pregnancy, puerperium and perinatal conditions	8	0.02(0.01, 0.04)	0.02(0.01, 0.04)	342.79	−5.48 (-6.42)	0.02(0.01)

drug concentration of sorafenib reaches a steady state after 7 days of administration, so adverse reactions related to sorafenib may be more easily observed after 7 days of taking the medication [40]. It is worth noting that a large portion of the data lacks specific times for the occurrence of adverse events, which limits our understanding of the occurrence of adverse events at different times of medication. Further research requires accurate medication time data and explores the difference in the response of the drug at different times of medication. Geographically, the majority of adverse event reports originate from the United States and Japan, both of which are developed nations with advanced healthcare systems. The higher economic standards in these countries likely contribute to the more widespread use of sorafenib, leading to an increased frequency of reported adverse events. However, a significant portion (57.67 %) of the reports come from unknown countries, indicating a need for further investigation to uncover potential regional or cultural biases that may affect the reporting and analysis of adverse events. The economic implications of sorafenib, like many other targeted therapies, are substantial. The high cost of this drug poses a significant financial burden on patients, particularly in low- and middle-income countries where healthcare resources are already limited. In these regions, the prohibitive cost of sorafenib may restrict patient access, exacerbating disparities in the availability of effective cancer treatments. This situation raises critical questions about the equity of access to essential therapies and highlights the importance of conducting cost-effectiveness analyses. Such analyses are crucial to better assess the value of sorafenib in relation to its clinical benefits, ensuring that its use is both economically sustainable and widely accessible across different healthcare settings.

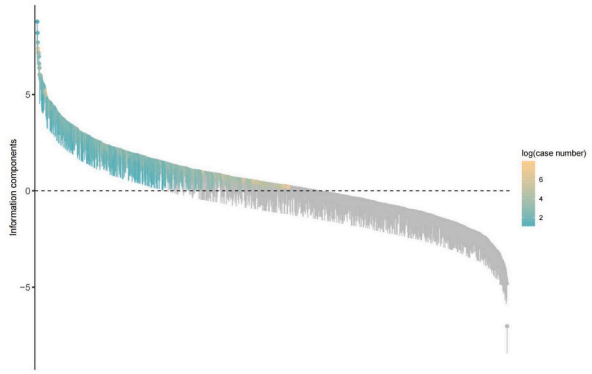

Fig. 3. Waterfall plot of all AEs signal intensities of PT level Sorafenib in the FAERS database.

As a targeted anti-tumor drug, sorafenib's adverse events primarily affect organ systems such as the skin and subcutaneous tissue, digestive system, cardiovascular system, lymphatic system, and immune system. Additionally, there are numerous reports involving the respiratory, endocrine, musculoskeletal, and nervous systems. Various infections and injuries are also common, underscoring the extensive scope of sorafenib's side effects, which align with its pharmacological actions and therapeutic indications. Given that sorafenib's targets on tumor cells may also be present in normal cells, the drug can significantly impact normal cellular functions. Moreover, sorafenib's ability to act on multiple targets simultaneously increases the potential for interactions with various cellular processes, potentially leading to a broader range of side effects.

In managing these adverse events, several strategies can be employed. For patients experiencing severe side effects, dose adjustments or temporary treatment interruptions may be necessary. For example, in cases of hand-foot skin reactions or severe diarrhea, reducing the dose or temporarily discontinuing sorafenib can help manage these symptoms while allowing the patient to continue benefiting from the treatment. Supportive care, such as the use of emollients for skin reactions and anti-diarrheal agents, can further alleviate these side effects. Regular monitoring of thyroid function is also recommended, as sorafenib may interfere with the synthesis, secretion, or metabolism of thyroid hormones. Early detection of thyroid abnormalities and appropriate management can prevent more serious complications.

Our in-depth review of sorafenib has uncovered that the most common and relatively specific adverse reactions to this class of tyrosine kinase inhibitors (TKIs) include hand-foot skin reactions, rashes, and digestive symptoms such as diarrhea and decreased appetite, findings that align with our study results [41]. Sorafenib's targeting of the epidermal growth factor receptor (EGFR) not only predisposes patients to skin lesions like rashes but also frequently induces diarrhea. As a multi-kinase inhibitor, it may also disrupt thyroid function by inhibiting kinases involved in the synthesis, secretion, or metabolism of thyroid hormones [42]. Furthermore, sorafenib's immunosuppressive effects, along with its impact on cellular metabolism and angiogenesis inhibition, largely account for the frequent injuries and infections observed [43]. These complex pathological processes underscore the necessity for further basic research to explore these adverse events in depth.

From the perspective of reported PTs, in addition to the most common skin reactions, digestive system discomfort, and thyroid disorders, our study also identified several adverse events not mentioned in the drug's labeling, such as vitamin K deficiency, elevated protein induced by vitamin K absence or antagonist II (PIVKA-II), abnormal alpha-fetoprotein levels, tumor metastasis, and splenic atrophy. Sorafenib may interfere with the metabolic pathway of vitamin K or reduce the liver's ability to synthesize proteins, leading to vitamin K deficiency and impaired coagulation factor production [44]. The abnormality of alpha-fetoprotein may be linked to tumor progression, particularly in HCC, which has a strong correlation with elevated alpha-fetoprotein levels [45]. Further research is needed to explore the relationship between sorafenib and alpha-fetoprotein. Currently, no direct evidence links sorafenib to tumor metastasis; this phenomenon may involve multiple factors, such as the tumor microenvironment and immune system function. Given sorafenib's effects on the immune system and angiogenesis, splenic lesions are plausible due to the spleen's role as an essential immune organ.

Our study also identified several rare yet highly signal-intensive adverse event reports, including chloracne, poorly differentiated thyroid carcinoma, liver carcinoma ruptured, reactive perforating collagenosis, and tumor thrombosis. The etiology of these events is likely multifactorial. Sorafenib may affect tissues highly dependent on the RAF/MEK/ERK signaling pathway, such as the skin [46], and its inhibition of VEGFR could impair normal vascular function, potentially leading to vascular-related adverse events like thrombosis [47]. Additionally, sorafenib may have unknown impacts on the immune system, potentially causing immune-related adverse events, including poorly differentiated thyroid carcinoma. The progression of the disease and its complications, such as liver carcinoma rupture, may also be correlated with the timing and stage of the disease during sorafenib administration.

Acknowledging inter-patient variability is crucial, as it can influence the pharmacokinetics and pharmacodynamics of the drug. To elucidate these rare adverse events, a comprehensive consideration of the aforementioned factors, along with in-depth epidemiological and clinical research, is essential. This approach will enhance our understanding of the causes of these adverse events and facilitate their proper management. The need for further research is highlighted by the complexity of these pathological processes and the potential for improved patient outcomes through a more nuanced understanding of sorafenib's effects.

It is crucial to underscore that further observational studies are necessary to elucidate the adverse reactions identified in this study

Table 5
The top 30 AEs signal strength of Sorafenib at the PTs level in FAERS database detected by four algorithms.

System organ class (SOC)	PTs	Case Reports	ROR(95 % CI)	PRR(95 % CI)	$\chi 2$	IC (IC025)	EBGM (EBGM05)
injury, poisoning and procedural complications	chloracne	3	1756.39 (182.69, 16886)	1756.32 (184.38, 16730.29)	1315.74	8.78 (6.88)	439.83 (66.2)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	poorly differentiated thyroid carcinoma	4	585.47 (146.42, 2341.07)	585.44 (145.59, 2354.22)	1166.89	8.2 (6.62)	293.22 (91.95)
investigations	protein induced by vitamin k absence or antagonist ii increased	17	321.12 (177.73, 580.2)	321.05 (178.32, 578.01)	3502.93	7.7 (6.92)	207.7 (126.61)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	hepatocellular carcinoma	1804	236.54 (223.89, 249.9)	231.15 (217.95, 245.15)	296419.44	7.38 (7.3)	166 (158.54)
investigations	alpha 1 foetoprotein increased	142	192.34 (159.11, 232.51)	191.99 (157.82, 233.56)	20317.11	7.18 (6.91)	144.83 (123.57)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	liver carcinoma ruptured	41	186.17(131, 264.57)	186.07 (130.75, 264.79)	5726.95	7.14 (6.66)	141.44 (105.4)
skin and subcutaneous tissue disorders	reactive perforating collagenosis	6	159.68 (64.74, 393.82)	159.67(64.81, 393.35)	743.31	6.97 (5.78)	125.67 (59.04)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	renal cell carcinoma stage iv	18	115.83 (69.86, 192.05)	115.8(69.57, 192.76)	1710.29	6.6(5.9)	96.84 (63.43)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	tumour thrombosis	23	96.9(62.33, 150.65)	96.87(61.72, 152.04)	1872.46	6.38 (5.76)	83.26 (57.56)
investigations	alpha 1 foetoprotein decreased	3	73.18(22.04, 243.04)	73.18(22.14, 241.9)	189.85	6.03 (4.51)	65.16 (23.87)
skin and subcutaneous tissue disorders	palmar-plantar erythrodysaesthesia syndrome	2109	73.98(70.67, 77.45)	72.03(69.26, 74.91)	131596.31	6.01 (5.94)	64.25 (61.84)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	tumour embolism	16	70.98(42.24, 119.25)	70.96(42.63, 118.12)	984.32	5.99 (5.26)	63.4(41.07)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	thyroid cancer metastatic	24	69.92(45.79, 106.78)	69.9(45.42, 107.58)	1456.16	5.97 (5.37)	62.55 (43.89)
injury, poisoning and procedural complications	hepatic rupture	17	68.65(41.54, 113.47)	68.64(41.23, 114.26)	1014.19	5.94 (5.24)	61.54 (40.42)
respiratory, thoracic and mediastinal disorders	hepatic hydrothorax	6	61.63(26.57, 142.94)	61.63(26.53, 143.16)	323.77	5.8 (4.68)	55.85 (27.63)
skin and subcutaneous tissue disorders	plantar erythema	19	56.77(35.44, 90.91)	56.75(35.45, 90.84)	948.66	5.7 (5.03)	51.83 (34.94)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastases to diaphragm	4	53.22(19.12, 148.13)	53.22(19.21, 147.47)	187.88	5.61 (4.28)	48.87 (20.75)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	tumour fistulisation	3	53.22(16.32, 173.55)	53.22(16.42, 172.51)	140.91	5.61 (4.12)	48.87 (18.18)
metabolism and nutrition disorders	food refusal	40	50.39(36.48, 69.6)	50.36(36.8, 68.91)	1781.95	5.54 (5.08)	46.45 (35.45)
reproductive system and breast disorders	scrotal irritation	3	50.18(15.43, 163.17)	50.18(15.48, 162.65)	133.19	5.53 (4.05)	46.3(17.26)
blood and lymphatic system disorders	spleen atrophy	3	50.18(15.43, 163.17)	50.18(15.48, 162.65)	133.19	5.53 (4.05)	46.3(17.26)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	tumour rupture	32	49.32(34.38, 70.75)	49.3(34.64, 70.16)	1396.66	5.51(5)	45.55 (33.68)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	huerthle cell carcinoma	3	48.79(15.02, 158.43)	48.79(15.05, 158.15)	129.62	5.5 (4.01)	45.11 (16.84)
skin and subcutaneous tissue disorders	palmoplantar keratoderma	44	48(35.29, 65.27)	47.97(35.06, 65.64)	1870.34	5.47 (5.04)	44.41 (34.34)
endocrine disorders	thyroid atrophy	4	46.84(16.92, 129.69)	46.84(16.9, 129.79)	166.14	5.44 (4.12)	43.44 (18.53)
nervous system disorders	coma hepatic	43	42.76(31.37, 58.29)	42.74(31.23, 58.48)	1633.6	5.32 (4.88)	39.9(30.79)

(*continued on next page*)

Table 5 (*continued*)

System organ class (SOC)	PTs	Case Reports	ROR(95 % CI)	PRR(95 % CI)	χ2	IC (IC025)	EBGM (EBGM05)
investigations	alpha 1 foetoprotein abnormal	6	42.32(18.48, 96.93)	42.32(18.58, 96.4)	225.75	5.31 (4.2)	39.54 (19.76)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	renal cell carcinoma	274	39.83(35.24, 45.02)	39.7(35.3, 44.65)	9680.17	5.22 (5.04)	37.24 (33.61)
nervous system disorders	hepatic encephalopathy	457	37.44(34.06, 41.17)	37.23(33.75, 41.06)	15152.19	5.13(5)	35.07 (32.39)
neoplasms benign, malignant and unspecified (incl cysts and polyps)	metastases to adrenals	39	34.56(25.02, 47.74)	34.54(25.24, 47.26)	1199.51	5.03 (4.57)	32.67 (24.93)

that are not currently documented in the drug's labeling. The discussion of sorafenib's adverse events and their potential mechanisms presented here remains speculative and warrants further investigation. Establishing a definitive causal relationship requires additional research and validation. The occurrence of adverse events is likely influenced by a multitude of factors, including the pharmacological properties of the drug, individual patient variability, and underlying comorbidities. Consequently, a more comprehensive understanding of these mechanisms will require in-depth experimental and clinical research. Meanwhile, it is imperative for healthcare professionals to consistently and meticulously monitor the emergence of adverse events in clinical practice and to implement timely intervention strategies when necessary.

In the next years, the field is expected to witness significant advancements in personalized medicine, with a focus on tailoring treatment strategies based on genetic and molecular profiles. Sorafenib's place in this evolving landscape will depend on ongoing research into its combinatorial potential with IO and other therapies, as well as continued monitoring of its long-term safety and efficacy. The integration of real-world data with prospective clinical trials will be crucial in refining treatment protocols and improving patient outcomes.

5. Limitations

This study provides valuable insights into the safety profile of sorafenib by utilizing the FAERS database, offering a real-world perspective on post-market adverse events. However, several limitations should be acknowledged. First, the FAERS database is based on spontaneous reporting, which is inherently subject to reporting bias, underreporting, and incomplete data. This can result in an overrepresentation of certain adverse events while underestimating others, particularly in regions or countries with less robust reporting mechanisms. Additionally, the FAERS database lacks long-term follow-up data, limiting our ability to assess the persistence and long-term effects of adverse events associated with sorafenib. This is particularly important for chronic conditions where long-term drug safety is a critical consideration. The voluntary nature of FAERS reporting also introduces the potential for inaccurate drug-ADE associations, as reports from non-professionals may lack the clinical detail necessary for precise causality assessments. Moreover, the database does not provide the total number of sorafenib users, precluding a comprehensive epidemiological analysis and accurate incidence rate calculations for adverse events. Finally, while our statistical methods are robust, they may still be prone to false positives, particularly as the number of reports increases. Future research should incorporate prospective studies and long-term clinical trials to validate these findings and offer more precise guidance for clinical practice.

6. Conclusion

To sum up, this study has mined the FAERS database from multiple perspectives and levels, and used a variety of algorithms to analyze the data from different levels, providing a solid scientific basis for the safety evaluation of sorafenib. Although the frequency of some adverse reactions (such as chloracne, splenic atrophy, etc.) is relatively low, its high signal intensity requires more attention and research. Our study also revealed several unique adverse reactions that were not explicitly mentioned in the drug manual, such as abnormal alpha-fetoprotein, tumor metastasis, etc. These findings suggest that medical professionals should be more cautious when using sorafenib for treatment, and patients should also be aware of these potential adverse reactions. Although our study has limitations, these research results undoubtedly provide valuable references for future in-depth drug research and safety regulatory work, and also provide more targeted guidance for clinical medication.

Data availability statement

The datasets analysed during the current study are available in the FAERS repository, [https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html].

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors agree to publication.

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CRediT authorship contribution statement

Lin Ning: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yuan Tian:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Di Chen:** Supervision, Software, Resources. **Jie Han:** Supervision, Software, Resources. **Guanyue Xie:** Supervision, Software, Resources. **Jianguang Sun:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37348.

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