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Adverse event profiles of selpercatinib: a real-world pharmacovigilance analysis based on FAERS database

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Abstract

Background Selpercatinib, a highly selective tyrosine kinase inhibitor, has emerged as an excellent treatment option for patients with rearranged during transfection-altered cancer. However, there is limited comprehensive safety information available for selpercatinib through large-scale post-marketing monitoring.

Methods This study conducted a comprehensive analysis of selpercatinib-related adverse events (AEs) using the FDA Adverse Event Reporting System database. Four disproportionality methods were employed to identify potential AEs associated with selpercatinib. Specifically, this study investigated the differences in AEs of selpercatinib with respect to reporter continent, indication, sex, age, weight, dose, frequency, and onset time.

Results A total of 464 reports and 1,007 selpercatinib-related AEs were identified. Three new significant AEs were discovered, including dysphagia, pericardial effusion, and hemiparesis. Notably, Asia reported hepatic function abnormal more frequently, especially in patient administered doses exceeding 160 mg. Furthermore, hypersensitivity was reported more frequently by Asia and in individuals weighing less than 50 kg.

Conclusions It is paramount to stay vigilant concerning the potential emergence of three newly identified AEs. Significant differences were found in selpercatinib-related AEs concerning reporter continent, sex, weight, dose, frequency, and onset time, which deserved clinical attention. These findings contribute to a broader understanding of the AE profiles of selpercatinib.

Highlight

- Three new significant adverse events were discovered, including dysphagia, pericardial effusion, and hemiparesis.
- Asia reported hepatic function abnormal more frequently, especially in patient administered single doses exceeding 160 mg.
- Hypersensitivity was reported more frequently by Asia and in individuals weighing less than 50 kg.

Keywords Selpercatinib, Adverse event, FAERS, Hepatobiliary disorders, Hypersensitivity

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Introduction

Activating rearranged during transfection (RET) alteration, such as gene fusion and mutation, can occur and lead to uncontrolled cellular proliferation [1]. It is a hallmark of cancer development, and plays a critical role in the development and progression of non-small cell lung

cancer, medullary thyroid carcinoma, thyroid cancer, hepatobiliary cancer, prostate cancer, breast cancer, and others [2, 3]. Statistically, oncogenic RET fusions are present in nearly 2% of patients with non-small cell lung cancer and 10–20% of patients with thyroid cancer [1]. In addition, RET mutations are drivers in 60% of sporadic medullary thyroid cancers and 99% of hereditary thyroid cancers [1]. However, the response rates of RET-altered cancers to traditional chemotherapy were relatively low [1]. Moreover, limited response and progression-free survival benefit has been shown with immunotherapy, possibly due to low levels of Programmed Death Ligand 1 expression and low mutation burden [1]. Till now, the treatment of RET-altered cancers remains quite challenging.

With the introduction of targeted therapies, the discovery, rapid clinical translation, and trials leading to Food and Drug Administration (FDA) approvals of selective RET inhibitors have witnessed significant advancements in the treatment of RET-altered cancers [2]. By blocking RET signaling pathways, the selective RET inhibitors, such as selpercatinib and pralsetinib, can effectively inhibit tumor growth, reduce the spread of cancer, and improve patient outcomes. This innovative approach has revolutionized the treatment of RET-altered cancers, offering new hope and improved outcomes for RET-altered cancer patients.

Selpercatinib, a highly selective tyrosine kinase inhibitor (TKI), is considered the first RET inhibitor for adults with metastatic or locally advanced solid tumors with RET gene alteration [4]. It has gained approval from the FDA for the treatment non-small cell lung cancer, medullary thyroid carcinoma, and thyroid cancer in May 2020 [5]. Current evidences have demonstrated promising results for selpercatinib, with significant tumor shrinkage and improved progression-free survival in patients with RET-altered pancreatic adenocarcinoma, colorectal, salivary, breast, soft-tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma [6–13]. As compared with cabozantinib and vandetanib, selpercatinib treatment resulted in superior progression-free survival and treatment failure-free survival [14, 15]. Additionally, within patients who have serious adverse events (AEs) or progressive disease after treating with pralsetinib, the therapeutic switch to selpercatinib eventually restored disease control [16]. Therefore, selpercatinib has emerged as an excellent treatment option for patients with RET-altered cancer who previously had limited options.

While the development of selpercatinib has improved survival, with its increasing use, it is crucial to be aware of AEs [17]. Currently, clinical trials have revealed the most prevalent AEs of selpercatinib, including edema, diarrhea, fatigue, dry mouth, abdominal pain, constipation, hypertension, rash, nausea, and headache [18]. Some serious AEs associated with selpercatinib have also been reported leading to dose reduction or treatment interruption, such as hypertension, elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), and severe gastrointestinal toxicity characterized by small bowel edema and lymphocytic duodenitis [19–21]. Cheng et al. enrolled 8 patients diagnosed with advanced non-small cell lung cancer and brain metastasis harboring a centrally confirmed RET fusion, who were treated with selpercatinib [22]. Of the 8 patients, 63% experienced grade > =3 AEs, with the severity of AEs assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [22]. However, clinical trials may not fully capture the real-world reactions to selpercatinib due to limited sample sizes, inadequate follow-up, strict study designs, and controlled conditions that differ from actual clinical practice [23]. It is crucial to gather comprehensive safety information on selpercatinib through extensive post-marketing monitoring in order to effectively manage potential AEs.

The United States FDA Adverse Event Reporting System (FAERS) stands as one of the largest pharmacovigilance databases worldwide [24]. It contains AEs associated with drugs and therapeutic biologics that have been spontaneously reported by consumers, physicians, pharmacists, and other health-professionals since 2004 [24]. In recent years, it has been utilized for post-marketing safety surveillance of various drugs such as capmatinib [23], alpelisib [25], romosozumab [26], lurbinectedin [27], bevacizumab [28], and upadacitinib [29]. To gain a better understanding of the AE profiles of selpercatinib in real-world settings, this study conducted a comprehensive analysis using the FAERS database, especially concerning the differences in AEs between different subgroups. This study contributes to a more comprehensive understanding of the AE profiles of selpercatinib.

Methods

Data source and collection

The FAERS database is regularly updated on a quarterly basis. For this study regarding selpercatinib, AE data were downloaded from the official United States FDA website covering the period from the third quarter of 2020 (2020Q3, July–September 2020) to the first quarter of 2023 (2023Q1, January-March 2023). The third quarter of 2020 marked the initial period during which AE reports associated with selpercatinib became detectable. The most recent AE data available at the time of this study pertained to the first quarter of 2023, which was published on April 27, 2023. Five types of datasets were

leveraged, including patient demographic and administrative information (DEMO), drug information (DRUG), therapy start dates and end dates for reported drugs (THER), indications for use/diagnosis (INDI), as well as coded for the AEs (REAC) [30]. Reports concerning selpercatinib were identified by searching for the term "SELPERCATINIB" in the "prod_ai" column, which displays the active ingredient of the product. The AE reports where selpercatinib was the "primary suspected" (PS) drug were included. All the AEs were coded using preferred terms (PT) and categorized to the corresponding primary system organ class (SOC) levels according to the standardized Medical Dictionary for Regulatory Activities (MedDRA) version 25.1 [31–33].

Statistical analysis

Descriptive analysis was used to characterize the clinical details reported upon the selpercatinib-associated AE reports, including report season, reporter continent, reporter country, indication, reporter type, sex, age, weight, dose, frequency, and onset time, after removing missing data [30–33]. Next, the relationship between dose and frequency in selpercatinib-associated AE reports, as well as their distribution across countries were examined.

The AE signals of selpercatinib were mined at the SOC and PT levels [30–33]. Four disproportionality methods were employed, including reporting odds ratio (ROR) [34, 35], proportional reporting ratio (PRR) [33, 36], Bayesian confidence propagation neural network (BCPNN) [33, 36, 37], and the multi-item gamma Poisson shrinker (MGPS) [33, 36, 37]. An AE signal of selpercatinib was identified if it met the criteria for the four algorithms concurrently [30–33]. Additionally, the differences in AE signals associated with selpercatinib were specifically investigated concerning reporter continent, indication, sex, age, weight, dose, frequency, and onset time subgroups using ROR algorithm and Fisher's exact test [30]. The fourfold tables, equations and criteria for signals detection and signal differences detection of selpercatinib are shown in Supplementary Tables S1-S4. All data processing and statistical analyses were conducted using Python 3 programming language in Jupyter Notebook version 6.4.12.

Results

Clinical characteristics analysis

In total, 464 reports and 1,007 AEs caused by selpercatinib were identified. A flow diagram depicting the data collection and analysis process for the selpercatinib-associated AEs is shown in Fig. 1.

Figure 2 shows the clinical characteristics of the 464 selpercatinib-associated AE reports. Overall, the number of selpercatinib-associated AE reports remained stable from quarter 3 of 2020 to quarter 1 of 2023, ranging from 30 to 59 cases per quarter with an average of 42.2 cases per quarter. The AE reports for selpercatinib were filed in 20 countries, covering 4 continents. Among the 463 valid records, 70.6% ($n=327$) of AE reports originated from the America and 70.0% ($n=324$) of AE reports were from

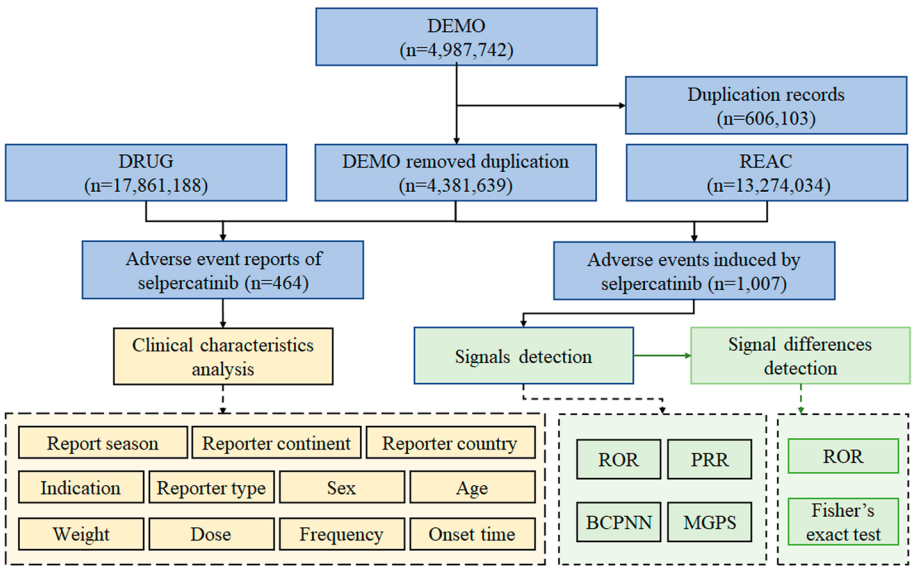

Fig. 1 Flow diagram of data collection and analysis of selpercatinib-associated adverse events. Abbreviations: DEMO, patient demographic and administrative information; DRUG, drug information; REAC, coded for the adverse events; ROR, reporting odds ratio; PRR, proportional reporting ratio; BCPNN, Bayesian confidence propagation neural network; MGPS, multi-item gamma Poisson shrinker

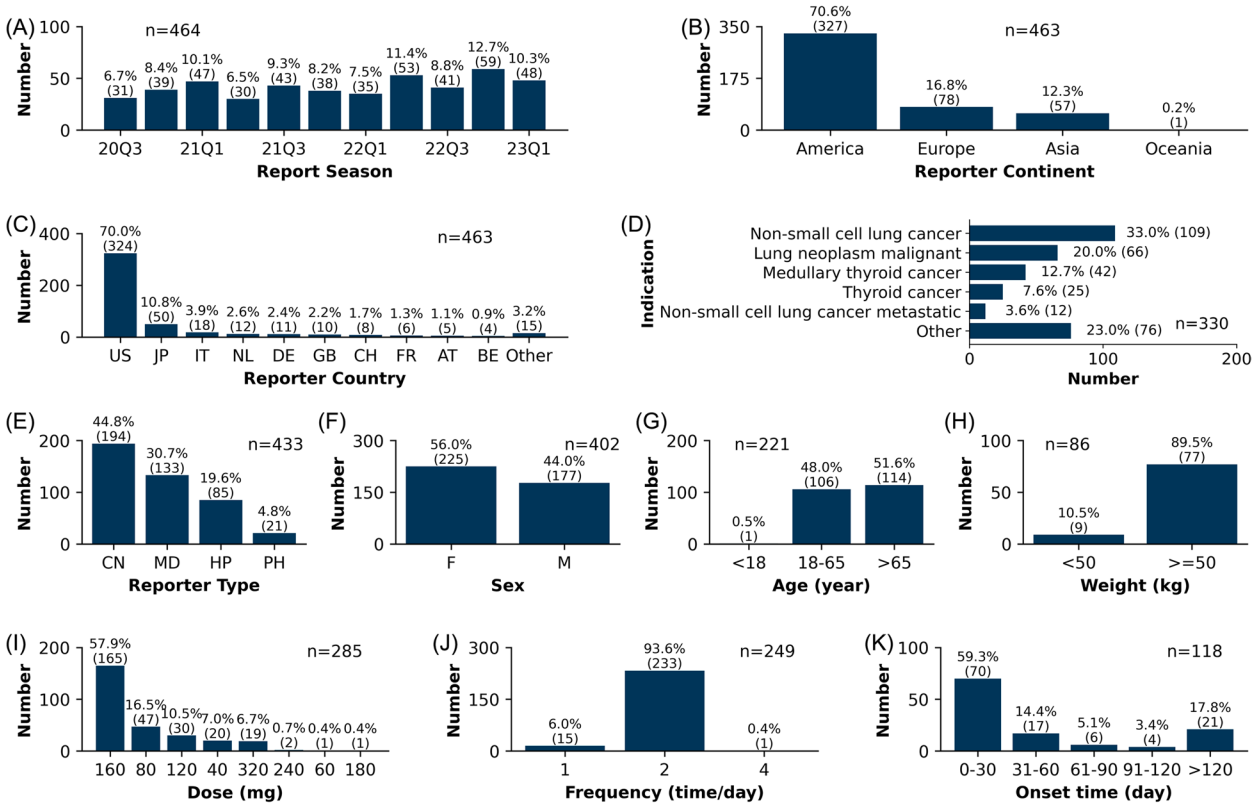

Fig. 2 Clinical characteristics of selpercatinib-associated AE reports. **A** Report season. **B** Reporter continent. **C** Reporter country. **D** Indication. **E** Reporter type. **F** Sex. **G** Age. **H** Weight. **I** Dose. **J** Frequency. **K** Onset time. Abbreviations: CN, Consumer; MD, Physician; HP, Health-professional; PH, Pharmacist; F, Female; M, Male; Abbreviations of countries can be found in Supplementary Table S5

the United States. Figure 2C displays the top 10 countries ranked by the number of reports. Number of reports and abbreviations of 20 countries can be found in Supplementary Table S5. The most prevalent indication was "non-small cell lung cancer" accounting for 33.0% ($n=109$) of the total valid cases. Other notable indications include "lung neoplasm malignant" with a prevalence of 20.0% ($n=66$), "medullary thyroid cancer" with 12.7% ($n=42$), and "thyroid cancer" with 7.6% ($n=25$). Excluding 31 reporters with unknown reporter type, consumers reported the most AE reports at 44.8% ($n=194$). Sex data was available for 402 cases. Of these, 56.0% ($n=225$) were female and 44.0% ($n=177$) were male. Age data was available for 221 cases, ranging from 16 to 94 years with a mean of 64.2 years. For reports with age data, 51.6% ($n=114$) were aged > 65 years, 48.0% ($n=106$) were aged 18–65 years, and only one patient was < 18 years. Valid weight data was available for only 86 patients, ranging from 40 to 118 kg with a mean of 67.8 kg. Of patients with weight data, 89.5% ($n=77$) weighed > =50 kg, while 10.5% ($n=9$) weighed < 50 kg.

Dosage adjustments of selpercatinib are recommended for managing adverse reactions while maintaining efficacy. In general, the recommended dosages of selpercatinib are 40, 80, 120, and 160 mg twice daily, as well as 40 mg once daily. Excluding missing data, non-comparable units, and unusual doses, 285 valid dose records were available. The single dose ranged from 40 to 320 mg with a mean of 145.1 mg. The most common dose was 160 mg, accounting for 57.9% ($n=165$) of records, followed by 80 mg (16.5%, $n=47$), 120 mg (10.5%, $n=30$), 40 mg (7.0%, $n=20$), and 320 mg (6.7%, $n=19$). For frequency, 249 valid records were available. Of these, 93.6% ($n=233$) were twice daily, 6.0% ($n=15$) were once daily, and 0.4% ($n=1$) were four times daily. Excluding false reports and missing data, 118 reports provided valid onset times for selpercatinib-associated AEs. Among these, 59.3% ($n=70$) of AEs occurred within 0-30 days of treatment.

The relationship between the dose and frequency groups was analyzed using parallel categories plot, as depicted in Fig. 3A. Based on the clinical characteristics of AE reports, the selpercatinib dose was categorized into five groups: 40, 80, 120, 160, and > 160 mg. The frequency of administration was divided into three groups: once-daily, twice-daily, and four times daily. The analysis revealed that the once-daily frequency, which is not

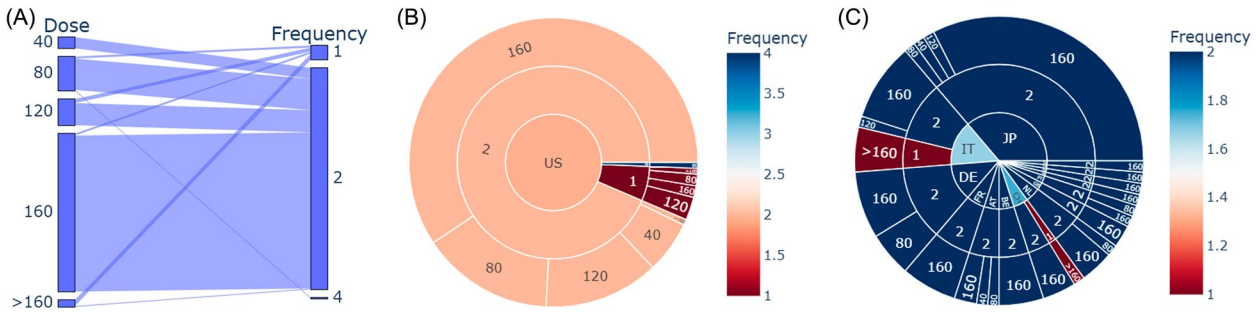

Fig. 3 Relationship between the dose and frequency across countries. **A** Parallel categories plot of dose and frequency. **B** Sunburst plot of dose and frequency distribution for the United States. **C** Sunburst plot of dose and frequency distribution for 14 countries. Abbreviations: Abbreviations of countries can be found in Supplementary Table S5

recommended in the clinic, was predominantly reported for single doses equal to or greater than 80 mg. A total of 235 cases concurrently provided information on the reporter country, dose, and frequency, encompassing 15 countries. The United States had the highest number of reports. Sunburst plots illustrating the dose and frequency distribution for the United States and other 14 countries are presented in Fig. 3B and C. The once-daily frequency was predominantly observed in the United States, Italy, and Switzerland. Conversely, the remaining 12 countries, including Japan, Germany, France, Austria, Belgium, Netherlands, Portugal, United Kingdom, Australia, Canada, China, and the United Arab Emirates, accurately had the dose and frequency in 100% of the reported cases.

Signals detection

The number and signal strength of selpercatinib at the SOC level are described in Table 1. Statistically, it was found that selpercatinib-associated AEs involved 26 SOCs. The significant SOC conforming to the criteria of four algorithms simultaneously was "hepatobiliary disorders" (SOC: 10019805).

A total of 37 signals at the PT level were detected after meeting four criteria. Among these, three signals including "malignant neoplasm progression" (PT: 10051398), "bone cancer" (PT: 10005949), and "therapy change" (PT: 10074300), which could potentially be attributed to disease progression, reduced therapeutic effect, or other factors, were considered unrelated to selpercatinib. The number and signal strength of 3 selpercatinib-unrelated signals at the PT level are listed in Supplementary Table S6. After excluding the 3 selpercatinib-unrelated signals, 34 selpercatinib-related signals are shown in Table 2. In terms of ROR, PRR, IC and EBGM values, the most significant AEs were "blood calcitonin increased" (PT: 10005390), "chylothorax" (PT: 10051228), and "ascites" (PT: 10003445). Furthermore, three significant AEs uncovered in the label and clinical trials of selpercatinib were highlighted, namely "dysphagia" (PT: 10013950), "pericardial effusion" (PT: 10034474), and "hemiparesis" (PT: 10019465).

Signal differences detection

Volcano plots generated by the ROR algorithm and Fisher's exact test, illustrating signal differences across reporter continent, indication, sex, age, weight, dose, frequency, and onset time, are depicted in Fig. 4. The analysis revealed no significant variation in selpercatinib-related signals between patients with lung cancer and thyroid cancer or between those aged 18–65 years and over 65 years. In comparison to America and Europe, Asia was more likely to report "hepatic function abnormal" (PT: 10019670), especially in patient administered doses exceeding 160 mg (America vs. Asia: ROR = 0.01, 95% CI [0.00–0.10], $P < 0.001$; Asia vs. Europe: ROR = 31.07, 95% CI [4.01–240.71], $P < 0.001$; doses > 160 mg vs. doses <= 160 mg: ROR = 6.46, 95% CI [1.61–25.88], $P = 0.023$). Notably, "hypersensitivity" (PT: 10020751) was more frequently to be reported by Asia and in individuals weighing less than 50 kg (America vs. Asia: ROR = 0.11, 95% CI [0.03–0.39], $P = 0.001$; Asia vs. Europe: ROR = 4.48, 95% CI [1.10–18.24], $P = 0.032$; weight < 50 kg vs. weight >= 50 kg: ROR = 21.88, 95% CI [1.89–253.92], $P = 0.023$).

Discussion

Currently, most of the information regarding the AEs associated with selpercatinib is derived from clinical trials. However, the AEs reported in clinical trials may not encompass the long-term or rare AEs that could encountered in clinical practice after selpercatinib is marketed. Furthermore, the differences in AEs related to selpercatinib among subgroups such as reporter continent, indication, sex, age, weight, dose, frequency, and onset time are still unclear. To overcome this limitation, this

Table 1 Number and signal strength of selpercatinib at the SOC level

SOC	Number	ROR		PRR		BCPNN		MGPS	
		ROR	Lower limit of 95% CI	PRR	χ2	IC	IC025	EBGM	EBGM05
General disorders and administration site conditions (SOC: 10018065)	174	0.98	0.83	0.98	0.06	-0.02	-0.26	0.98	0.83
Investigations (SOC: 10022891)[abc]	126	2.26	1.88	2.10	77.67	1.07	0.79	2.10	1.75
Gastrointestinal disorders (SOC: 10017947)[ac]	113	1.52	1.25	1.46	17.66	0.54	0.25	1.46	1.20
Nervous system disorders (SOC: 10029205)	74	1.04	0.82	1.03	0.09	0.05	-0.30	1.03	0.82
Skin and subcutaneous tissue disorders (SOC: 10040785)	58	1.18	0.91	1.17	1.54	0.23	-0.16	1.17	0.90
Respiratory, thoracic and mediastinal disorders (SOC: 10038738)[a]	58	1.32	1.01	1.30	4.23	0.38	-0.02	1.30	1.00
Infections and infestations (SOC: 10021881)	51	0.91	0.68	0.91	0.46	-0.13	-0.54	0.91	0.69
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC: 10029104)	45	0.85	0.63	0.86	1.10	-0.22	-0.65	0.86	0.64
Hepatobiliary disorders (SOC: 10019805)[abcd]	43	5.68	4.18	5.48	158.66	2.45	1.87	5.48	4.04
Blood and lymphatic system disorders (SOC: 10005329)[ac]	32	1.92	1.35	1.89	13.61	0.92	0.37	1.89	1.33
Musculoskeletal and connective tissue disorders (SOC: 10028395)	32	0.59	0.42	0.61	8.57	-0.72	-1.21	0.61	0.43
Vascular disorders (SOC: 10047065)[ac]	29	1.58	1.09	1.56	5.97	0.64	0.08	1.56	1.08
Injury, poisoning and procedural complications (SOC: 10022117)	28	0.21	0.14	0.23	81.21	-2.11	-2.62	0.23	0.16
Metabolism and nutrition disorders (SOC: 10027433)	23	1.25	0.82	1.24	1.08	0.31	-0.30	1.24	0.82
Cardiac disorders (SOC: 10007541)	22	1.14	0.75	1.13	0.36	0.18	-0.44	1.13	0.74
Eye disorders (SOC: 10015919)	21	1.12	0.73	1.12	0.28	0.17	-0.47	1.12	0.73
Surgical and medical procedures (SOC: 10042613)	20	1.45	0.93	1.44	2.69	0.52	-0.14	1.44	0.92
Immune system disorders (SOC: 10021428)	17	1.58	0.98	1.57	3.55	0.65	-0.08	1.57	0.97
Psychiatric disorders (SOC: 10037175)	16	0.27	0.16	0.28	31.15	-1.83	-2.47	0.28	0.17
Renal and urinary disorders (SOC: 10038359)	11	0.57	0.31	0.57	3.63	-0.81	-1.60	0.57	0.31
Ear and labyrinth disorders (SOC: 10013993)	4	1.01	0.38	1.01	0.00	0.01	-1.29	1.01	0.38
Endocrine disorders (SOC: 10014698)	3	1.17	0.38	1.17	0.07	0.22	-1.28	1.17	0.38
Pregnancy, puerperium and perinatal conditions (SOC: 10036585)	2	0.61	0.15	0.61	0.51	-0.72	-2.19	0.61	0.15
Reproductive system and breast disorders (SOC: 10038604)	1	0.17	0.02	0.17	3.95	-2.53	-3.80	0.17	0.02
Product issues (SOC: 10077536)	1	0.05	0.01	0.06	16.41	-4.17	-5.30	0.06	0.01
Social circumstances (SOC: 10041244)	1	0.20	0.03	0.20	3.12	-2.29	-3.60	0.20	0.03

The depth of color corresponds to the magnitude of the value, with darker shades indicating larger values

SOC system organ class, *ROR* reporting odds ratio, *CI* confidence interval, *PRR* proportional reporting ratio, *χ2* chi-squared, *BCPNN* Bayesian confidence propagation neural network, *IC* information component, *IC025* lower limit of 95% confidence interval of IC, *MGPS* multi-item gamma Poisson shrinker, *EBGM* empirical Bayesian geometric mean, *EBGM05* lower limit of 95% confidence interval of EBGM

[a] SOCs met the criteria of ROR algorithm

[b] SOCs met the criteria of PRR algorithm

[c] SOCs met the criteria of BCPNN algorithm

[d] SOCs met the criteria of MGPS algorithm

study conducted a comprehensive analysis of AEs that reported after the post-marketing period of selpercatinib.

This study identified 34 signals related to selpercatinib, most of which were consistent with information from the drug label. Three new significant signals were discovered, including "dysphagia", "pericardial effusion", and "hemiparesis". The limited number of cases may account for their absence in previous trials. Currently, no studies linking these signals to selpercatinib have been found. Nevertheless, insights from studies on other anticancer drugs may offer some context. For example, Zhang et al. described a case in which a patient developed dysphagia while undergoing erlotinib treatment, attributed to compression by enlarged mediastinal lymph nodes [38]. Moreover, dysphagia and hemiparesis could potentially be neurological symptoms related to brain metastases, which can be improved or resolved with effective treatment [39]. Amano et al. documented a disease flare in a patient with lung adenocarcinoma who experienced hemiparesis due to new, rapidly growing brain metastases

Table 2 Number and signal strength of selpercatinib at the PT level

PT	Number	ROR		PRR		BCPNN		MGPS	
		ROR	Lower limit of 95% CI	PRR	χ2	IC	IC025	EBGM	EBGM05
General disorders and administration site conditions (SOC: 10018065)									
Death (PT: 10011906)	44	3.24	2.39	3.14	65.03	1.65	1.14	3.14	2.32
Pyrexia (PT: 10037660)	20	3.82	2.45	3.76	40.77	1.91	1.10	3.76	2.42
Oedema peripheral (PT: 10030124)	10	8.13	4.36	8.06	61.83	3.01	1.42	8.05	4.32
Oedema (PT: 10030095)	7	10.78	5.12	10.71	61.60	3.42	1.25	10.70	5.09
Skin and subcutaneous tissue disorders (SOC: 10040785)									
Rash (PT: 10037844)	26	3.89	2.64	3.82	54.39	1.93	1.22	3.82	2.58
Gastrointestinal disorders (SOC: 10017947)									
Ascites (PT: 10003445)	17	42.81	26.48	42.10	680.26	5.39	2.99	41.97	25.97
Dry mouth (PT: 10013781)	17	16.89	10.46	16.63	249.61	4.05	2.47	16.61	10.28
Dysphagia (PT: 10013950)*	6	4.98	2.23	4.95	18.95	2.31	0.57	4.95	2.22
Vascular disorders (SOC: 10047065)									
Hypertension (PT: 10020772)	17	5.28	3.27	5.21	57.93	2.38	1.39	5.20	3.22
Investigations (SOC: 10022891)									
Aspartate aminotransferase increased (PT: 10003481)	15	23.75	14.26	23.41	321.41	4.55	2.56	23.37	14.03
Alanine aminotransferase increased (PT: 10001551)	13	16.72	9.67	16.52	189.44	4.04	2.19	16.50	9.54
Liver function test increased (PT: 10077692)	9	21.46	11.13	21.28	173.72	4.41	1.89	21.25	11.02
Electrocardiogram QT prolonged (PT: 10014387)	6	10.28	4.60	10.22	49.90	3.35	1.05	10.21	4.58
Blood creatinine increased (PT: 10005483)	6	6.34	2.84	6.31	26.82	2.66	0.75	6.31	2.83
Blood calcitonin increased (PT: 10005390)	3	1802.74	538.71	1797.38	4739.80	10.63	0.44	1581.81	472.69
Transaminases increased (PT: 10054889)	3	8.55	2.75	8.53	19.92	3.09	0.12	8.52	2.74
Blood alkaline phosphatase increased (PT: 10059570)	3	13.25	4.26	13.21	33.84	3.72	0.26	13.20	4.25
Blood bilirubin increased (PT: 10005364)	3	10.03	3.23	10.00	24.30	3.32	0.17	10.00	3.22
Blood and lymphatic system disorders (SOC: 10005329)									
Thrombocytopenia (PT: 10043554)	14	8.51	5.02	8.41	91.49	3.07	1.74	8.40	4.96
Leukopenia (PT: 10024384)	4	5.62	2.10	5.60	15.11	2.48	0.25	5.60	2.10
Lymphopenia (PT: 10025327)	3	11.62	3.74	11.59	29.02	3.53	0.22	11.58	3.73
Hepatobiliary disorders (SOC: 10019805)									
Hepatic function abnormal (PT: 10019670)	13	23.07	13.34	22.79	270.47	4.51	2.38	22.75	13.16
Hepatotoxicity (PT: 10019851)	11	27.07	14.94	26.79	272.66	4.74	2.25	26.74	14.75
Liver disorder (PT: 10024670)	4	6.17	2.31	6.15	17.27	2.62	0.30	6.15	2.30
Hypertransaminasaemia (PT: 10068237)	4	32.12	12.02	31.99	119.82	5.00	0.86	31.92	11.94
Immune system disorders (SOC: 10021428)									
Hypersensitivity (PT: 10020751)	13	4.52	2.61	4.47	35.13	2.16	1.06	4.47	2.59
Respiratory, thoracic and mediastinal disorders (SOC: 10038738)									
Pleural effusion (PT: 10035598)	11	14.16	7.81	14.02	132.95	3.81	1.91	14.00	7.73
Pulmonary oedema (PT: 10037423)	4	6.56	2.46	6.54	18.76	2.71	0.34	6.53	2.45
Chylothorax (PT: 10051228)	3	298.20	94.80	297.31	866.41	8.18	0.52	290.77	92.44
Pneumonitis (PT: 10035742)	3	6.73	2.17	6.71	14.58	2.75	0.02	6.71	2.16
Cardiac disorders (SOC: 10007541)									
Pericardial effusion (PT: 10034474)*	4	12.11	4.53	12.07	40.58	3.59	0.61	12.06	4.51
Nervous system disorders (SOC: 10029205)									
Subarachnoid haemorrhage (PT: 10042316)	4	33.41	12.50	33.28	124.96	5.05	0.86	33.20	12.42
Hemiparesis (PT: 10019465)*	3	15.15	4.88	15.11	39.49	3.92	0.29	15.09	4.86
Metabolism and nutrition disorders (SOC: 10027433)									
Hypocalcaemia (PT: 10020947)	3	11.16	3.59	11.13	27.65	3.48	0.21	11.12	3.58

Table 2 (continued)

The colors of the individual table cells represent the values of each index

PT preferred term, *ROR* reporting odds ratio, *CI* confidence interval, *PRR* proportional reporting ratio, *χ2* chi-squared, *BCPNN* Bayesian confidence propagation neural network, *IC* information component, *IC025* lower limit of 95% confidence interval of IC, *MGPS* multi-item gamma Poisson shrinker, *EBGM* empirical Bayesian geometric mean, *EBGM05* lower limit of 95% confidence interval of EBGM

[a] Emerging findings of selpercatinib-induced AEs

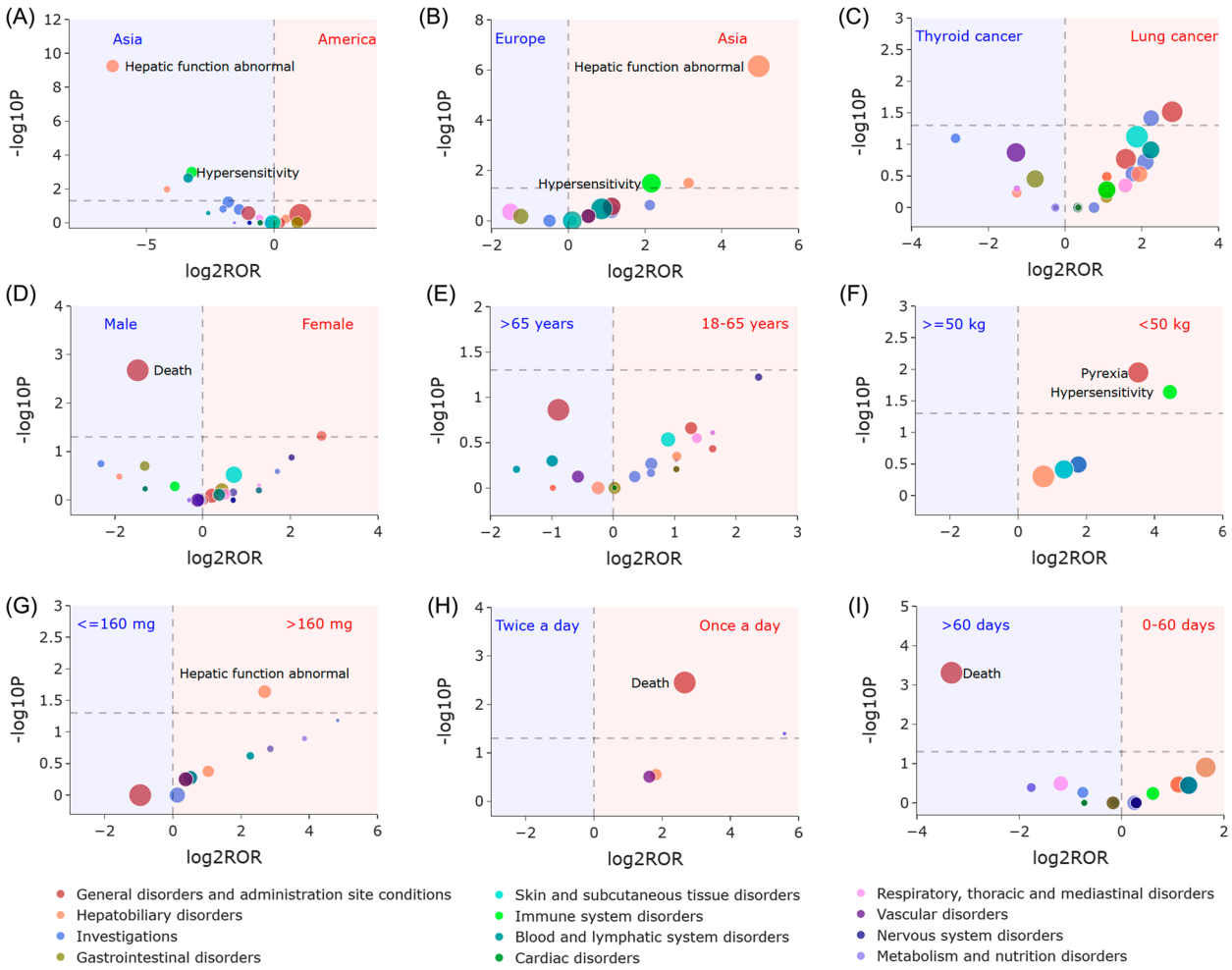

Fig. 4 Volcano plots for signal differences of selpercatinib. **A** Signal differences between America and Asia. **B** Signal differences between Asia and Europe. **C** Signal differences between patients with lung cancer and thyroid cancer. **D** Signal differences between females and males. **E** Signal differences between patients with age 18–65 years and > 65 years. **F** Signal differences between patients with weight < 50 kg and > = 50 kg. **G** Signal differences between dose > 160 mg and dose < = 160 mg. **H** Signal differences between frequency once a day and twice a day. **I** Signal differences between onset time 0–60 days and onset time > 60 days. The colors of each point represent different SOCs. The sizes of each point represent the report numbers of each PT induced by selpercatinib. In these volcano plots, signals within 34 significant disproportionality PTs of selpercatinib are shown

after discontinuing crizotinib [40]. Base on the findings, promptly monitor for lymph nodes and disease flares in the brain are recommended when dysphagia and hemiparesis are detected during selpercatinib use. This study suggests maintaining vigilance for the potential occurrence of these newly discovered AEs related to selpercatinib, and elucidating this association through further research.

Chylous effusions, though rare, have been observed in patients undergoing selpercatinib treatment. As per the label of selpercatinib, the incidences of chylous effusions, encompassing chylothorax and chylous ascites, are both

below 2% [41]. However, recent studies by independent researchers suggest a higher incidence rate. A retrospective multicenter study documented spontaneous chylous effusions in individuals receiving selpercatinib, with the incidence escalating to 7% [42]. Notably, Provenzano et al. treated 16 selpercatinib patients since June 2019, with 25% of cases presenting with ascites [43]. In this study, the high signal strength of "chylothorax" and "ascites" further corroborates these findings. Managing chylous effusions presents challenges as they can arise or worsen unpredictably during treatment without an apparent cause [44, 45]. Differential diagnosis is essential to prevent misattributing it as progressive malignancy through a variety of methods, such as imaging, paracentesis, and fluid triglyceride level measurements [42, 46]. For symptomatic and/or moderate to severe cases with chylous effusions, effective management options include dose reduction of selpercatinib, fluid aspiration, a high-protein low-fat diet, and monthly octreotide injections [44, 46]. These findings suggest the necessity to strengthen the diagnosis and management of chylous effusions when using selpercatinib.

"Hepatobiliary disorders" emerged as the single SOC satisfying all four criteria, with the most prominent PT being "hepatic function abnormal". Specifically, Asia and patients taking doses exceeding 160 mg exhibited a significantly higher reporting frequency of "hepatic function abnormal" (America vs. Asia: ROR = 0.01, 95% CI [0.00–0.10], $P < 0.001$; Asia vs. Europe: ROR = 31.07, 95% CI [4.01–240.71], $P < 0.001$; doses > 160 mg vs. doses < = 160 mg: ROR = 6.46, 95% CI [1.61–25.88], $P = 0.023$). In instances of liver function impairment events lacking overt clinical symptoms, assessing ALT and AST levels assumes critical importance. For grade 2 or below liver dysfunction associated with selpercatinib, the management can involve dose reductions [19]. In cases of grade 3 or higher liver dysfunction, a temporary suspension of selpercatinib treatment is advised. These findings underscore the necessity of evaluating liver function pre-treatment initiation and ongoing monitoring during treatment, particularly for Asian populations and individuals on high selpercatinib doses.

Hypersensitivity poses a potential concern linked to selpercatinib use, with reported rates of selpercatinib-related hypersensitivity ranging from 6–7% [41, 47]. Similar to other TKIs, hypersensitivity predominantly manifested in patients previously treated with immune checkpoint inhibitors (ICIs) [47]. In a phase 1/2 LIBRETTO-001 trial, hypersensitivity reactions to selpercatinib were more prevalent in patients with prior ICI exposure (77%) compared to ICI-naive patients (23%) [47]. Moreover, this study indicated that Asian populations and individuals weighing less than 50 kg had a higher report frequency of "hypersensitivity" (America vs. Asia: ROR = 0.11, 95% CI [0.03–0.39], $P = 0.001$; Asia vs. Europe: ROR = 4.48, 95% CI [1.10–18.24], $P = 0.032$; weight < 50 kg vs. weight > = 50 kg: ROR = 21.88, 95% CI [1.89–253.92], $P = 0.023$). To ensure correct treatment, medical professionals must be well-versed in recognizing and managing hypersensitivity syndrome related to selpercatinib, which can be effectively managed with supportive care measures and is reversible [48]. The current recommended approach involves initiating systemic corticosteroids (oral prednisone) at a dose of 1 mg/kg daily, or equivalent, with appropriate prophylaxis [48]. Treatment can continue until symptoms resolve, following which selpercatinib may be reintroduced at a reduced dose below the level that triggered the hypersensitivity reaction [47]. If even a dose as low as 40 mg twice daily is intolerable, discontinuation of selpercatinib is advised [47]. These findings underscore the critical need for monitoring and managing hypersensitivity reactions, particularly in prior ICI-treated patients, Asian populations, and individuals with lower body weight.

Treatment-related hypertension is a well-known AE of TKIs, including selpercatinib (> 25%) [41]. In this study, "hypertension" was the only significant PT related to SOC "vascular disorders". The results did not show significant differences in selpercatinib-related hypertension among different subgroups. It is recommended that hypertensive patients have their blood pressure levels under control before starting selpercatinib and regularly monitored thereafter. For patients with slight increases in blood pressure or grade 1 hypertension, non-pharmacological approaches such as lifestyle changes should be implemented [49]. Patients with grade 2 or 3 hypertension should receive antihypertensive treatment, such as diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. It should be noted that antihypertensive drugs like diuretics can cause QT interval prolongation [50]. Therefore, follow-up monitoring of blood pressure and QT prolongation is recommended for hypertensive patients, especially when taking selpercatinib in combination with certain antihypertensive drugs.

Despite only three reported cases, "blood calcitonin increased" emerged as the most significant signal based on ROR, PRR, IC, and EBGM values. This study further analyzed the indications for reports of "blood calcitonin increased". Two of these cases were linked to indications: "medullary thyroid cancer" and "thyroid cancer", and one case had no reported indication. Serum calcitonin serves as a valuable tumor marker in patients with medullary thyroid carcinoma [51]. However, another article suggests that high serum calcitonin levels are not specific to medullary thyroid cancer [52]. Due to the small number

of reports, longer term studies are needed to verify the relevance of this signal to the use of selpercatinib.

Regarding indications, no significant signal variations were observed between lung cancer and thyroid cancer. In a non-small cell lung cancer trial of selpercatinib, notable grade 3 or above AEs were hypertension (14%), increase in the ALT level (12%), and increase in the AST level (10%) [53]. Another trial focusing on advanced ret-mutant medullary thyroid cancer revealed hypertension (18.7%), increase in the ALT level (10.4%), and increase in the AST level (4.7%) as the most common grade 3 or above AEs [54]. Present evidence doesn't advocate for specific AE management strategies when employing selpercatinib for lung cancer and thyroid cancer.

There were fewer reported AEs in males compared to females. This aligns with the well-known epidemiological feature that the number of lung cancer and thyroid cancer cases is higher in females than in males. In the United States, the estimated number of new cases of lung cancer was higher in females (120,790) than in males (117,550), and the estimated number of new thyroid cancer patients was also higher in females (31,180) than in males (12,540) in 2023 [55]. A global post-marketing surveillance study, drawing on aggregated evidence from individual case reports collected worldwide over half a century, indicated that females, particularly from puberty onward and notably during their reproductive years, tend to report more adverse reactions than males [56]. Moreover, a higher proportion of serious and fatal adverse reactions were noted in male reports [56]. These results underscore the importance of considering sex as a critical factor throughout the course of selpercatinib use, with particular emphasis on the serious AEs in males.

The relationship between the dose and frequency groups indicated that once-daily dosing was primarily reported for single doses of 80 mg or higher. Such dosing approaches, predominantly observed in the United States, Italy, and Switzerland, were not recommended. It is advised to divide the total daily dose into two administrations. Suydam et al. reported a case of a 13-year-old female diagnosed with metastatic papillary thyroid carcinoma. After two dose reductions of selpercatinib for possibly related weight, the patient responded well to a dosage of 80 mg twice daily [57]. These findings emphasize the importance of medical professionals being vigilant in adjusting dosages. Selpercatinib is available in two dosage strengths: 40 mg and 80 mg. It is explicitly stated in the label that selpercatinib should be swallowed whole and should not be crushed or chewed. Therefore, doses such as 60 mg and 180 mg are not permitted. In a case involving a 43-year-old advanced non-small cell lung cancer patient diagnosed with a rare RET gene fusion, a modified selpercatinib dosage (160 mg in the morning and 80 mg in the evening) was used with good tolerance and without compromising effectiveness [17]. This case suggests that in certain situations, a modified selpercatinib dosage outside the label (such as using different doses in the morning and evening) may provide a safe and effective alternative, rather than crushing or chewing it. These results emphasize the importance of adjusting selpercatinib to a reasonable individualized dosage to minimize serious AEs.

It should be noted that the time period of this study included the COVID-19 pandemic period where access to healthcare and AE reporting was unusual [58]. Cancer patients who contract COVID-19 should exercise heightened caution when using selpercatinib, and critically ill COVID-19 patients should consider temporarily discontinuing selpercatinib. Additionally, oral antiviral medications for COVID-19, such as azvudine and nirmatrelvir/ritonavir, may interact with selpercatinib. Azvudine has the potential to cause lymphocytopenia, elevated blood bilirubin levels, and increased ALT levels. When azvudine is used alongside selpercatinib, enhanced monitoring for hepatobiliary disorders and other relevant investigations is advisable. Selpercatinib is primarily metabolized by CYP3A4. Concurrent administration of selpercatinib with ritonavir, a potent CYP3A4 inhibitor, can substantially elevate the serum concentration of selpercatinib. Additional research is warranted to establish the AE profile of selpercatinib under normal circumstances.

Disproportionality analyses used in signal detection for spontaneous reports are broadly categorized into two groups: frequency count methods, such as ROR, PRR, and the Medicines and Healthcare Products Regulatory Agency (MHRA), and Bayesian methods, such as BCPNN and MGPS algorithms [37]. To address potential biases, recent studies have increasingly utilized combinations of multiple algorithms in data analysis. Among these, the simultaneous use of two commonly-used frequency count methods (ROR and PRR) and two representative prominent Bayesian methods (BCPNN and MGPS) has been widely applied. Therefore, this study selected these four algorithms to investigate potential associations between adverse event signals and the use of selpercatinib. It is noteworthy that while we face the intrinsic bias in favor of studies with positive results, we might also face the potential for false positive results arising from multiple testing [59]. The primary limitation of these studies rests in the detection threshold, which ideally ought to have been adjusted in accordance with the number of hypotheses [59]. This limitation is also applicable to this study. Apart from algorithm selection, the choice of a comparator is of significant importance in disproportionality analysis. However, determining the

most suitable comparator for pharmacovigilance still lacks clear standards [60]. For instance, selpercatinib and pralsetinib are selective RET inhibitors with similar market exposure durations. Nevertheless, similar to selpercatinib, the adverse events associated with pralsetinib are also not yet fully understood. The literature notes that even if a comparator effectively mitigates one bias, its concurrent impact on other biases remains uncertain and often unobservable [60]. Drawing from prevailing literature on FAERS database management, this study compared the reporting rates of selpercatinib with rates across all other drugs. However, in future research, it remains crucial to select appropriate comparators for further investigation of adverse events associated with selpercatinib.

It is important to acknowledge the limitations of this study. Firstly, consumers were the main source of AEs information. Relying on the non-professional reporters could potentially impact the accuracy of the reported data. To distinguish between AEs caused by the disease itself and those caused by selpercatinib, the judgments should be made based on clinical experience and literature. Secondly, with a limited number of valid cases for certain clinical characteristics, there could be a wide range in CI of the ROR value. For example, while a previous study suggested that advanced age might be a risk factor for hepatic disorders [61], this study did not observe significant differences in this regard, necessitating continued attention from clinicians regarding age-related differences. Thirdly, the study primarily drew data from developed countries such as the United States, Japan, and Italy, where selpercatinib is more accessible. Consequently, the absence of AE data from developing countries limits the generalizability of the findings. Fourthly, the study was unable to calculate the incidence of AEs induced by selpercatinib due to the absence of information on the total number of medication users, which is crucial for accurately assessing the safety of selpercatinib. Fifthly, the study did not consider the effects of potential confounding factors that could influence the occurrence of AEs, such as concomitant medication, comorbidities and type of RET change [62]. For instance, while traditional Chinese medicines have been found to have antineoplastic effects, liver protection, nervous system protection, and cardiovascular protection [63–65], this study lacked such information. In future research, it remains crucial to take into account potential confounding factors for further in-depth understanding of adverse events with selpercatinib. Sixthly, it is important to note that signal detection does not prove a causal relationship between the drug and the AEs, and cannot fully overcome the inherent limitations of spontaneous reporting systems or replace expert reviews. All the results presented in this study only indicate statistical correlations, necessitating further research to validate the findings and draw definitive conclusions. Despite these limitations, this study plays a significant role in promoting the rational use of selpercatinib and provides important insights into its AE profiles.

Conclusions

This study conducted a comprehensive analysis of selpercatinib using the FAERS database. The analysis identified three previously unrecognized AEs, including dysphagia, pericardial effusion, and hemiparesis, that may manifest in patients using selpercatinib. It is recommended to conduct liver function examinations, particularly for Asian populations and individuals on high doses of selpercatinib. Furthermore, medical professionals should maintain heightened vigilance in monitoring hypersensitivity reactions, especially in Asians and individuals with lower body weight. Overall, this study contributes to a broader understanding of the AE profiles of selpercatinib.

Abbreviations

RET	Rearranged during transfection
FDA	Food and Drug Administration
TKI	Tyrosine kinase inhibitor
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CTCAE	Cancer Institute Common Terminology Criteria for Adverse Events
FAERS	Food and Drug Administration Adverse Event Reporting System
PS	Primary suspected
PT	Preferred terms
SOC	System organ class
MedDRA	Medical Dictionary for Regulatory Activities
ROR	Reporting odds ratio
PRR	Proportional reporting ratio
BCPNN	Bayesian confidence propagation neural network
MGPS	Multi-item gamma Poisson shrinker
CI	Confidence interval
ICI	Immune checkpoint inhibitor

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

JQ and SZ wrote the first draft, and participated in data analyses and interpretation. CJ contributed to conception and study design, and revisions of the manuscript. All authors reviewed the manuscript, and approved the final version.

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Data availability
Raw data for this article can be downloaded at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html; further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable. Ethical approval was not required for this study because we used the FAERS database, which is a free open-access database.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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