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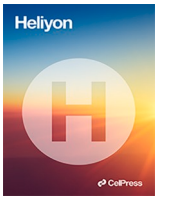

Research article

# A disproportionality analysis of sunitinib in the FDA adverse event reporting system (FAERS)

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A B S T R A C T

*Objective:* This study aimed to analyze the FAERS database to identify adverse event associated with sunitinib to offer valuable insights for the judicious utilization of medication in clinical settings.

*Methods:* Various disproportionality analysis techniques, such as the reporting odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPN), and multi-gamma Poisson shrinkage (MGPS), were employed to analyze adverse drug reaction (ADR) reports pertaining to sunitinib in the FAERS database from its market introduction up to the first quarter of 2023. Subsequently, a secondary screening process was conducted to identify reliable positive signals.

*Results:* The analysis of sunitinib adverse event signals at the system-organ classification level encompassed 27 organ systems, with gastrointestinal and endocrine disorders emerging as the predominant SOCs. A total of 237 significant adverse events meeting all four algorithms were detected. Notably, this study revealed previously unreported adverse events, including pleural effusion and ascites, while potential adrenal toxicity-related adverse events, highlighted in the drug's specification, were not identified in this analysis. The study examined the relationship between the duration of sunitinib dosing and the onset of adverse events, revealing a median onset of 48 days (IQR, 15–160 days). The findings indicated that a majority of adverse events manifested early in the dosing period, with tumor progression, disease progression, and mortality becoming more prevalent after one year of treatment.

*Conclusion:* In the clinical utilization of sunitinib, vigilant monitoring of potential adverse reactions is imperative during the initial phase of drug administration. In addition to the documented adverse reactions outlined in the drug specification, healthcare providers should remain attentive to potential adverse reactions such as pleural effusion, ascites, and tumor development.

## 1. Introduction

Sunitinib, a multi-target tyrosine kinase inhibitor, demonstrates efficacy in inhibiting a range of receptors including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) α and β, c-kit, and other associated receptors [1]. This mechanism allows for the inhibition of angiogenic and proliferative processes in tumors, thereby exhibiting potent anti-tumor effects. Sunitinib has been FDA-approved since 2006 for the treatment of advanced renal cell carcinoma (mRCC) in adult patients, gastrointestinal mesenchymal stromal tumors (GIST) that have not responded to or are intolerant to imatinib mesylate, and

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unresectable, metastatic, highly differentiated progressive pancreatic neuroendocrine tumors (pNET) [2]. Despite receiving approvals for the aforementioned indications, ongoing studies are being conducted on sunitinib in various other tumors such as gastric cancer [3], breast cancer [4], thyroid carcinoma [5,6], hepatocellular carcinoma [7], thymic carcinoma [8] and lung cancer [9]. According to findings from a multicenter study published in *The Lancet* in 2024, sunitinib has demonstrated significant promise in the management of metastatic progressive pheochromocytoma and paraganglioma [10]. Nevertheless, as sunitinib becomes more commonly utilized in clinical settings, there is a growing concern regarding its safety. Literature suggests that prevalent adverse events (AEs) linked to sunitinib encompass fatigue, hypertension, nausea, vomiting, and hand and foot rash [2]. A number of other side effects of sunitinib have been identified as more clinical trials have been conducted. In Phase III studies in patients with GIST or metastatic RCC, cardiotoxicity (primarily left ventricular insufficiency.) was seen in approximately 11 %–16 % of patients treated with sunitinib [11–13]. Hypothyroidism has also been found to be a side effect of sunitinib, with rates ranging from 4 % to 16 % reported in Phase III studies [11,12]. Diarrhoea occurs frequently in patients treated with sunitinib, with rates ranging from 29 % to 53 % in Phase III studies [11–13]. Most patients with metastatic RCC treated with sunitinib experience some form of haematological toxicity [11,14]. In addition, sunitinib can induce several rare toxic reactions such as gastrointestinal perforation, colonic emphysema, rheumatoid arthritis, encephalopathy syndrome, chronic wounds, and hypophosphatemia [15]. Currently, the evidence for sunitinib-related side effects is mainly derived from phase III clinical trials and related Meta-analyses, To better investigate the overall safety profile of sunitinib medication, we conducted this study based on a large sample size of real-world data.

The Food and Drug Administration's Adverse Event Reporting System (FAERS) database serves as a reputable repository for gathering AEs on a global scale, offering a crucial information source for drug safety surveillance and accurately depicting the safety profile of medications in practical settings [16]. The significance of this database is paramount, as it serves as a crucial resource for clinicians and researchers seeking to enhance their comprehension of the safety characteristics associated with various pharmaceutical agents.

Due to the extensive utilization of sunitinib and its possible AEs, it is imperative to undertake thorough safety investigations and analysis of sunitinib utilizing the FAERS database. The objective of this research is to comprehensively investigate the adverse event profiles associated with sunitinib based on data from the FAERS database, in order to offer a more comprehensive and rigorous safety guideline for clinical practice.

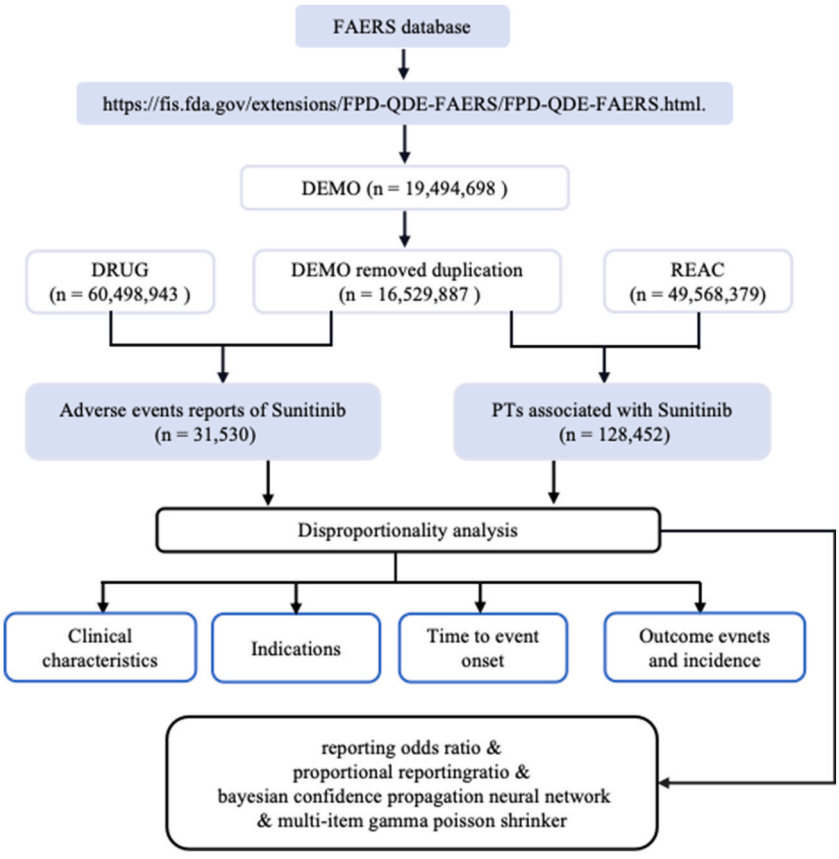


**Fig. 1.** The flow diagram of selecting adverse events reports of sunitinib from FAERS database.

## 2. Methods

### 2.1. Data sourcing and extraction

The objective of this research is to analyze the adverse event (AE) data of sunitinib in real-world scenarios. The specific flow of data extraction is illustrated in Fig. 1. A dataset comprising 19,494,698 AE reports sourced from the FAERS database spanning the period from the first quarter of 2004 to the first quarter of 2023 was utilized for analysis, with the data being retrieved from https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The FAERS database contained seven categories of raw data, including demographic and administrative information (DEMO), drug details (DRUG), adverse event (REAC), patient outcomes (OUTC), report sources (RPSR), start and end dates for reported drugs (THER), and indications for use (INDI).

The AE preferred terms (PTs) and system organ classes (SOCs) were systematically categorized and aligned with the MedDRA dictionary. The extracted data underwent censorship in accordance with the data screening guidelines outlined by the FDA, resulting in a total of 16,529,887 AE reports. A total of 60,498,943 DRUG_files and 49,568,379 REAC_files were incorporated into the study. The DRUG_files encompassed four distinct categories of drug information: primary suspect (PS), secondary suspect (SS), concomitant (C), and interaction (I). The database was queried using both the trade and generic names of sunitinib, resulting in the retrieval of 31,530 reports documenting AEs with sunitinib as the PS, as well as 128,452 PTs for AEs linked to sunitinib.

**Table 1**
The characteristics of adverse events reports with sunitinib from the FAERS database (Q1 2006 - Q1 2023).

| Characteristics | Reports number (n) | Reports proportion (%) |
|---|---|---|
| Number of events | 31530 | |
| Gender | | |
| Female | 10073 | 31.95 % |
| Male | 18970 | 60.16 % |
| Unknown | 2487 | 7.89 % |
| Age (year) | | |
| < 18 | 4 | 0.01 % |
| 18≤ and < 65 | 163 | 0.52 % |
| ≥65 | 172 | 0.55 % |
| Unknown | 31191 | 98.92 % |
| Median (IQR) | 65 ( 55,71 ) | |
| Reporting countries(top five) | | |
| American(US) | 16654 | 52.82 % |
| China(CN) | 1746 | 5.54 % |
| Argentina(AR) | 1611 | 5.11 % |
| India(IN) | 1396 | 4.43 % |
| Brazil(BR) | 1183 | 3.75 % |
| Occupation of reporters | | |
| Consumer | 13461 | 42.69 % |
| Physician | 8453 | 26.81 % |
| Pharmacist | 2825 | 8.96 % |
| Health professional | 513 | 1.63 % |
| Other health porfessional | 5262 | 16.69 % |
| Lawyer | 4 | 0.01 % |
| Unknown | 1012 | 3.21 % |
| Indications ( top five ) | | |
| Metastatic renal cell carcinoma | 6561 | 20.81 % |
| Renal cell carcinoma | 5052 | 16.02 % |
| Renal cancer | 4106 | 13.02 % |
| Gastrointestinal stromal tumour | 2350 | 7.45 % |
| Renal cancer metastatic | 1216 | 3.86 % |
| Outcomes | | |
| Death | 9315 | 29.54 % |
| Life-threatening | 159 | 0.50 % |
| Hospitalization | 5979 | 18.96 % |
| Disablity | 198 | 0.63 % |
| Congenital anomaly | 3 | 0.01 % |
| Required intervention to prevent | 22 | 0.07 % |
| Other medical event | 6878 | 21.81 % |
| Unknown | 8976 | 28.47 % |
| Reporting year, n(%) | | |
| 2006–2010 | 5196 | 16.48 % |
| 2011–2015 | 12659 | 40.15 % |
| 2016–2020 | 11218 | 35.58 % |
| 2021-2023Q1 | 2457 | 7.79 % |

### 2.2. Data analysis

Descriptive analyses were employed to thoroughly examine reports of adverse events to sunitinib, with a specific focus on gender disparities in reporting, age demographics, reporting countries, occupation of reporters, indications, adverse event outcomes, reporting years, and time to onset. Time to adverse event was operationally defined as the duration between the date of the adverse event and the initial use of sunitinib.

This study evaluated the signal strength of various adverse events to sunitinib through the application of commonly utilized disproportional analysis techniques, which included the reporting advantage ratio (ROR), the proportional reporting ratio (PRR), the Bayesian Confidence Propagation Neural Network (BCPNN), and the Multi Gamma Poisson Shrinker (MGPS), with the particular formulas and screening criteria employed for this analysis outlined in Table S1. Signals that satisfy any one of the four established

**Table 2**
FAERS database signal strength of sunitinib adverse event reports at System organ class (SOC) level.

| System Organ Class(SOC) | Sunitinib Cases Reporting SOC | ROR (95 % Two-Sided CI) | PRR($\chi^2$) | EBGM (EBGM05) | IC(IC025) | Significance |
|---|---|---|---|---|---|---|
| General disorders and administration site conditions | 26,240 | 1.22(1.21–1.24) | 1.18(844.23) | 1.18(1.16) | 0.23 (−1.43) | ** |
| Gastrointestinal disorders | 22,921 | 2.33(2.29–2.36) | 2.09 (14151.57) | 2.08(2.05) | 1.06 (−0.61) | *** |
| Investigations | 10,518 | 1.34(1.31–1.36) | 1.31(812.41) | 1.31(1.28) | 0.39 (−1.28) | ** |
| Skin and subcutaneous tissue disorders | 9863 | 1.47(1.44–1.50) | 1.43(1361.2) | 1.43(1.40) | 0.52 (−1.15) | ** |
| Nervous system disorders | 8959 | 0.80(0.78–0.81) | 0.81(439.43) | 0.81(0.79) | −0.30 (−1.97) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 6442 | 1.87(1.83–1.92) | 1.83 (2477.83) | 1.83(1.78) | 0.87 (−0.80) | ** |
| Respiratory, thoracic and mediastinal disorders | 5813 | 0.95(0.93–0.98) | 0.95(13.58) | 0.95(0.93) | −0.07 (−1.73) | |
| Metabolism and nutrition disorders | 4907 | 1.78(1.73–1.83) | 1.75 (1612.22) | 1.75(1.70) | 0.81 (−0.86) | ** |
| Musculoskeletal and connective tissue disorders | 4841 | 0.70(0.68–0.72) | 0.71(588.34) | 0.71(0.69) | −0.49 (−2.15) | |
| Injury, poisoning and procedural complications | 4409 | 0.33(0.32–0.33) | 0.35 (5959.47) | 0.35(0.34) | −1.52 (−3.19) | |
| Infections and infestations | 4042 | 0.59(0.57–0.61) | 0.6(1106.69) | 0.60(0.59) | −0.73 (−2.39) | |
| Vascular disorders | 3400 | 1.22(1.18–1.26) | 1.22(132.27) | 1.21(1.17) | 0.28 (−1.39) | ** |
| Blood and lymphatic system disorders | 3260 | 1.54(1.48–1.59) | 1.52(593.84) | 1.52(1.47) | 0.61 (−1.06) | ** |
| Psychiatric disorders | 2525 | 0.33(0.32–0.34) | 0.34 (3347.26) | 0.34(0.33) | −1.54 (−3.20) | |
| Renal and urinary disorders | 2400 | 0.95(0.91–0.99) | 0.95(5.88) | 0.95(0.91) | −0.07 (−1.74) | |
| Cardiac disorders | 2224 | 0.63(0.61–0.66) | 0.64(465.84) | 0.64(0.61) | −0.65 (−2.31) | |
| Eye disorders | 1418 | 0.56(0.53–0.59) | 0.56(495.77) | 0.56(0.53) | −0.83 (−2.50) | |
| Hepatobiliary disorders | 1383 | 1.18(1.12–1.24) | 1.18(37.14) | 1.18(1.12) | 0.23 (−1.43) | ** |
| Endocrine disorders | 917 | 2.88(2.70–3.08) | 2.87 (1112.02) | 2.86(2.68) | 1.51 (−0.15) | *** |
| Reproductive system and breast disorders | 541 | 0.45(0.42–0.49) | 0.46(354.24) | 0.46(0.42) | −1.13 (−2.80) | |
| Surgical and medical procedures | 432 | 0.26(0.24–0.28) | 0.26(912.79) | 0.26(0.24) | −1.93 (−3.60) | |
| Immune system disorders | 348 | 0.25(0.22–0.27) | 0.25(804.71) | 0.25(0.22) | −2.01 (−3.68) | |
| Ear and labyrinth disorders | 335 | 0.60(0.54–0.66) | 0.6(90.98) | 0.60(0.54) | −0.74 (−2.41) | |
| Social circumstances | 225 | 0.37(0.33–0.43) | 0.38(235.01) | 0.38(0.33) | −1.41 (−3.08) | |
| Product issues | 45 | 0.02(0.02–0.03) | 0.02 (1901.05) | 0.02(0.02) | −5.44 (−7.11) | |
| Congenital, familial and genetic disorders | 38 | 0.09(0.07–0.13) | 0.09(331.45) | 0.09(0.07) | −3.40 (−5.07) | |
| Pregnancy, puerperium and perinatal conditions | 6 | 0.01(0.00–0.02) | 0.01(559.41) | 0.01(0.00) | −6.56 (−8.23) | |

methods may be classified as positive signals related to sunitinib. In order to mitigate the presence of false positives, only signals that concurrently adhere to all four aforementioned algorithms were chosen for subsequent analysis in this study.

The FAERS database is accessible in both ASCII and XML formats. In this study, ASCII-formatted data were employed for statistical analysis. Categorical variables were evaluated through frequencies and percentages, while continuous variables were assessed using medians and ranges. Trends in the time to onset of adverse events to sunitinib treatment were analyzed using Kaplan-Meier curves. Data processing and analysis were conducted using SAS 9.4 Vision, Microsoft Excel 2019, and SPSS Statistics 21.

We followed the recently developed recommendations for disproportionality analyses for the detection of drug safety signals using case safety reports in pharmacovigilance (READUS-PV) to support transparent and clear reporting of scientific findings [17,18], and the READUS-PV checklist is organised in Table S2.

## 3. Results

### 3.1. Clinical characteristic

A comprehensive analysis of AE reports linked to sunitinib in the FAERS database spanning from the first quarter of 2004 to the first quarter of 2023 revealed a total of 31,530 cases. After filtering out reports with missing data, an analysis revealed a skewed distribution of sexes in the reports, with a ratio of 60.16 % males to 31.95 % females. The reports contained a significant amount of missing age data, with the majority of known information indicating that patients over the age of 65 were most commonly reported, followed by those aged 18 to 65. Only four reports included patients under the age of 18, and the median age of the reports was 65 years (IQR, 55–71 years). The United States reported the highest number of AEs, with 16,654 cases accounting for 52.82 % of the total, followed by China (n = 1,746, 5.54 %), Argentina (n = 1,611, 5.1 %), India (n = 1,396, 4.43 %), and Brazil (n = 1,183, 3.75 %). Consumers spontaneously reported 13,461 (42.69 %) AE reports, followed by physicians (n = 8,453, 26.81 %), other health professionals (n = 5,262, 16.69 %), pharmacists (n = 2,825, 8.96 %), and health professionals (n = 513, 1.63 %). The top five indications with the highest number of reported cases and corresponding percentage of AEs were as follows: Metastatic renal cell carcinoma (n = 6,561, 20.81 %), Renal cell carcinoma (n = 5,052, 16.02 %), Renal cancer (n = 4,106, 13.02 %), Gastrointestinal stromal tumour (n = 2,350, 7.45 %), and Renal cancer metastatic (n = 1,216, 3.86 %). Detailed data are shown in Table 1.

### 3.2. Adverse event signals at system organ class (SOC) and prefer term (PT) level

The distribution of sunitinib signal at the SOC level encompassed 27 organ systems, with Gastrointestinal disorders (SOC: 10017947) and Endocrine disorders (SOC: 10014698) emerging as the most prominent SOCs, as indicated in Table 2. The analysis of disproportionality using the ROR and PRR revealed positive signals for some SOCs, including General disorders and administration site conditions (SOC: 10018065), Investigations (SOC: 10022891), Skin and subcutaneous tissue disorders (SOC: 10040785), Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC: 10029104), Metabolism and nutrition disorders (SOC: 10027433), Vascular disorders (SOC: 10047065), Blood and lymphatic system disorders (SOC: 10005329), and Hepatobiliary disorders (SOC: 10019805). These findings suggest that these signals may be of significance or occur frequently.

Based on the analytical methodology employed in this research, a total of 237 significant PTs were identified that satisfied all four algorithms, as depicted in Table 3. These AEs were classified as sunitinib-related AEs. The predominant AEs outlined in the patient instruction manual for individuals utilizing sunitinib were all notable PT signals, such as Decreased appetite (PT: 10061428), Neoplasm progression (PT: 10061309), Dysgeusia (PT: 10013911), Hypertension (PT: 10020772), Stomatitis (PT: 10042128), Palmar-plantar erythrodysaesthesia syndrome (PT: 10033553), Blood pressure increased (PT: 10005750), Oral pain (PT: 10031009), Platelet count decreased (PT: 10035528), Dyspepsia (PT: 10013946), Thrombocytopenia (PT: 10043554), Pyrexia (PT: 10037660), Blister (PT: 10005191), Epistaxis (PT: 10015090), Yellow skin (PT: 10048245), and others.

The insert for sunitinib highlighted a range of potentially severe AEs, such as hepatotoxicity, left ventricular dysfunction, haemorrhage, thyroid insufficiency, and adrenal abnormalities. Additionally, several pharmacovigilance terms, including Jaundice (PT: 10023126), Blood bilirubin abnormal (PT: 10058477), Renal haemorrhage (PT: 10038460), Tumour haemorrhage (PT: 10049750), Anal haemorrhage (PT: 10049555), Penile haemorrhage (PT: 10034305), Nail bed bleeding (PT: 10048891), Cardiopulmonary failure (PT: 10051093), Central hypothyroidism (PT: 10086754), and Thyroid atrophy (PT: 10043693) were consistently documented in this study. Notably, this study did not identify any AEs associated with adrenal function. Furthermore, the study observed AEs, such as pleural effusion (PT: 10035598) and ascites (PT: 10003445), which were not included in the sunitinib insert, underscoring the necessity for clinical vigilance.

### 3.3. Time to onset

The duration of dosing and time to onset of sunitinib-related AEs were obtained from the database, with 8588 AE reports providing details. The median time to onset was found to be 48 days (IQR, 15–160 days) as shown in Fig. 2A. According to the data presented in Fig. 2B, the frequency of AEs varied across different time periods: 0–30 days (n = 3471, 40.56 %), 30–60 days (n = 1178, 13.77 %), 60–180 days (n = 1972, 23.05 %), and 180–360 days (n = 932, 10.89 %). Interestingly, the occurrence of AEs remained significant even after one year of sunitinib treatment, accounting for 12.10 % of the data collected.

Additionally, through the calculation of the ROR values for AEt signals with varying onset times, it was determined that the top 20 PTs with the highest number of AE reports, excluding Death, exhibited AEs within the 0–30 day time range. Furthermore, the lower

**Table 3**
FAERS database signal strength of sunitinib adverse event reports at the Preferred Term (PT) level.

| SOC | PT | Reports | ROR, 95%Cl | PRR($\chi^2$) | EBGM (EBGM05) | IC (IC025) |
|---|---|---|---|---|---|---|
| General disorders and administration site conditions | Death | 6535 | 3.94(3.84–4.04) | 3.79 (13467.63) | 3.76(3.67) | 1.91 (0.25) |
| | Disease progression | 3689 | 17.14 (16.58–17.72) | 16.68 (52201.66) | 16.03(15.5) | 4.00 (2.34) |
| | Mucosal inflammation | 387 | 7.30(6.60–8.08) | 7.29(2060.63) | 7.17(6.48) | 2.84 (1.18) |
| | Organ failure | 39 | 4.39(3.20–6.02) | 4.39(100.82) | 4.35(3.17) | 2.12 (0.45) |
| | Performance status decreased | 35 | 3.46(2.48–4.83) | 3.46(60.69) | 3.44(2.46) | 1.78 (0.12) |
| | Pneumatosis | 5 | 5.23(2.16–12.64) | 5.23(16.87) | 5.17(2.14) | 2.37 (0.70) |
| Gastrointestinal disorders | Stomatitis | 1295 | 10.78 (10.20–11.40) | 10.68 (11070.21) | 10.42(9.86) | 3.38 (1.72) |
| | Oral pain | 1073 | 23.41 (22.00–24.90) | 23.22 (21526.41) | 21.96(20.64) | 4.46 (2.79) |
| | Dyspepsia | 764 | 3.80(3.54–4.08) | 3.78(1550.62) | 3.75(3.5) | 1.91 (0.24) |
| | Glossodynia | 571 | 13.35 (12.28–14.52) | 13.3(6280.12) | 12.89(11.85) | 3.69 (2.02) |
| | Ascites | 319 | 5.07(4.54–5.67) | 5.06(1027.39) | 5.01(4.49) | 2.33 (0.66) |
| | Mouth ulceration | 252 | 5.97(5.27–6.76) | 5.96(1025.02) | 5.89(5.2) | 2.56 (0.89) |
| | Oral discomfort | 249 | 8.54(7.53–9.68) | 8.52(1617.57) | 8.36(7.37) | 3.06 (1.40) |
| | Gingival pain | 162 | 9.91(8.47–11.58) | 9.89(1262.91) | 9.67(8.27) | 3.27 (1.61) |
| | Oral mucosal blistering | 148 | 11.09(9.42–13.06) | 11.08(1319.4) | 10.8(9.17) | 3.43 (1.77) |
| | Gingival bleeding | 118 | 4.40(3.67–5.28) | 4.4(306.49) | 4.36(3.64) | 2.12 (0.46) |
| | Tongue disorder | 110 | 6.64(5.50–8.02) | 6.64(518.01) | 6.54(5.42) | 2.71 (1.04) |
| | Aphthous ulcer | 104 | 5.15(4.25–6.25) | 5.15(343.23) | 5.09(4.2) | 2.35 (0.68) |
| | Tongue discomfort | 98 | 12.39 (10.13–15.15) | 12.38(993.19) | 12.02(9.83) | 3.59 (1.92) |
| | Oral disorder | 74 | 4.41(3.51–5.54) | 4.41(192.68) | 4.37(3.47) | 2.13 (0.46) |
| | Mouth haemorrhage | 72 | 4.76(3.77–6.01) | 4.76(211.31) | 4.71(3.74) | 2.24 (0.57) |
| | Glossitis | 66 | 8.77(6.87–11.19) | 8.77(443.98) | 8.59(6.73) | 3.10 (1.44) |
| | Proctalgia | 60 | 4.38(3.39–5.64) | 4.37(154.45) | 4.34(3.36) | 2.12 (0.45) |
| | Tongue blistering | 57 | 11.62(8.93–15.13) | 11.62(537.06) | 11.31(8.69) | 3.50 (1.83) |
| | Haemorrhoidal haemorrhage | 44 | 4.00(2.97–5.39) | 4(98.1) | 3.97(2.95) | 1.99 (0.32) |
| | Gingival swelling | 42 | 4.36(3.22–5.91) | 4.36(107.62) | 4.32(3.19) | 2.11 (0.45) |
| | Tongue discolouration | 37 | 3.59(2.60–4.97) | 3.59(68.62) | 3.57(2.58) | 1.84 (0.17) |
| | Anal haemorrhage | 37 | 6.37(4.60–8.82) | 6.37(164.74) | 6.28(4.54) | 2.65 (0.98) |
| | Oesophageal ulcer | 35 | 4.11(2.95–5.74) | 4.11(81.57) | 4.08(2.92) | 2.03 (0.36) |
| | Chapped lips | 34 | 3.73(2.66–5.23) | 3.73(67.27) | 3.7(2.64) | 1.89 (0.22) |
| | Gingival disorder | 33 | 3.81(2.70–5.37) | 3.81(67.68) | 3.78(2.68) | 1.92 (0.25) |
| | Gastrointestinal toxicity | 31 | 3.73(2.62–5.31) | 3.73(61.21) | 3.7(2.6) | 1.89 (0.22) |
| | Tongue ulceration | 28 | 3.76(2.59–5.45) | 3.76(56.05) | 3.73(2.57) | 1.90 (0.23) |

(*continued on next page*)

**Table 3** (*continued*)

| SOC | PT | Reports | ROR, 95%Cl | PRR($\chi^2$) | EBGM (EBGM05) | IC (IC025) |
|---|---|---|---|---|---|---|
| | Anorectal disorder | 25 | 5.79(3.90–8.60) | 5.79(97.59) | 5.72(3.85) | 2.52 (0.85) |
| | Lip blister | 24 | 4.09(2.73–6.11) | 4.09(55.34) | 4.05(2.71) | 2.02 (0.35) |
| | Lip pain | 22 | 3.60(2.37–5.48) | 3.6(40.9) | 3.57(2.35) | 1.84 (0.17) |
| | Pneumatosis intestinalis | 21 | 3.63(2.36–5.58) | 3.63(39.63) | 3.6(2.35) | 1.85 (0.18) |
| | Gingival recession | 20 | 5.11(3.28–7.94) | 5.1(65.15) | 5.05(3.25) | 2.34 (0.67) |
| | Oral mucosal erythema | 20 | 6.30(4.05–9.80) | 6.3(87.73) | 6.21(3.99) | 2.64 (0.97) |
| | Anal ulcer | 20 | 12.60(8.07–19.67) | 12.6(206.8) | 12.23(7.83) | 3.61 (1.94) |
| | Noninfective gingivitis | 18 | 5.83(3.66–9.29) | 5.83(70.98) | 5.76(3.62) | 2.53 (0.86) |
| | Oral mucosal eruption | 16 | 5.22(3.19–8.55) | 5.22(53.84) | 5.16(3.15) | 2.37 (0.70) |
| | Oesophageal haemorrhage | 16 | 5.51(3.36–9.02) | 5.51(58.21) | 5.44(3.32) | 2.44 (0.78) |
| | Tongue dry | 15 | 5.23(3.14–8.71) | 5.23(50.62) | 5.17(3.11) | 2.37 (0.70) |
| | Tongue erythema | 15 | 9.99(5.98–16.68) | 9.99(118.26) | 9.76(5.85) | 3.29 (1.62) |
| | Gingival discomfort | 15 | 13.27(7.93–22.21) | 13.27(164.54) | 12.86(7.69) | 3.69 (2.01) |
| | Reflux gastritis | 14 | 5.95(3.51–10.08) | 5.95(56.74) | 5.87(3.46) | 2.55 (0.89) |
| | Anal inflammation | 13 | 10.88(6.27–18.88) | 10.88(113.4) | 10.61(6.11) | 3.41 (1.74) |
| | Oral mucosal exfoliation | 12 | 3.63(2.06–6.42) | 3.63(22.7) | 3.61(2.04) | 1.85 (0.18) |
| | Rectal ulcer | 10 | 4.03(2.16–7.51) | 4.03(22.51) | 3.99(2.14) | 2.00 (0.33) |
| | Tongue exfoliation | 10 | 12.62(6.72–23.69) | 12.62(103.59) | 12.25(6.53) | 3.61 (1.94) |
| | Gastrointestinal fistula | 9 | 4.69(2.43–9.06) | 4.69(25.85) | 4.65(2.41) | 2.22 (0.55) |
| | Angular cheilitis | 8 | 6.46(3.21–12.98) | 6.46(36.27) | 6.37(3.16) | 2.67 (1.00) |
| | Oral mucosal roughening | 6 | 12.83(5.69–28.94) | 12.83(63.33) | 12.45(5.52) | 3.64 (1.96) |
| | Oesophagitis haemorrhagic | 5 | 7.49(3.09–18.14) | 7.49(27.57) | 7.36(3.04) | 2.88 (1.21) |
| | Rectal lesion | 4 | 13.51(4.98–36.60) | 13.5(44.75) | 13.08(4.83) | 3.71 (2.02) |
| | Hernial eventration | 3 | 8.81(2.81–27.69) | 8.81(20.32) | 8.64(2.75) | 3.11 (1.43) |
| | Pancreatic duct obstruction | 3 | 9.09(2.89–28.57) | 9.09(21.11) | 8.91(2.83) | 3.15 (1.47) |
| Investigations | Blood pressure increased | 1101 | 3.37(3.18–3.58) | 3.35(1807.95) | 3.33(3.14) | 1.74 (0.07) |
| | Platelet count decreased | 1046 | 4.75(4.47–5.05) | 4.72(3035.06) | 4.68(4.4) | 2.23 (0.56) |
| | Blood thyroid stimulating hormone increased | 143 | 7.34(6.22–8.66) | 7.33(767.18) | 7.21(6.11) | 2.85 (1.18) |
| | Blood urine present | 138 | 3.32(2.81–3.93) | 3.32(221.69) | 3.3(2.79) | 1.72 (0.06) |
| | Thyroid function test abnormal | 102 | 10.80(8.87–13.15) | 10.79(881.8) | 10.53(8.65) | 3.40 (1.73) |
| | Blood albumin decreased | 61 | 3.54(2.75–4.55) | 3.54(110.09) | 3.52(2.73) | 1.81 (0.15) |
| | Protein total decreased | 35 | 4.29(3.08–5.99) | 4.29(87.44) | 4.26(3.05) | 2.09 (0.42) |
| | Blood urine | 16 | 7.53(4.59–12.35) | 7.53(88.84) | 7.4(4.51) | 2.89 (1.22) |
| | Blood bilirubin abnormal | 14 | 5.78(3.41–9.80) | 5.78(54.55) | 5.71(3.37) | 2.51 (0.85) |

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**Table 3** (*continued*)

| SOC | PT | Reports | ROR, 95%Cl | PRR($\chi^2$) | EBGM (EBGM05) | IC (IC025) |
|---|---|---|---|---|---|---|
| | Thyroid hormones increased | 10 | 5.10(2.73–9.51) | 5.1(32.51) | 5.04(2.7) | 2.33 (0.67) |
| | Nutritional condition abnormal | 8 | 5.58(2.78–11.21) | 5.58(29.63) | 5.51(2.74) | 2.46 (0.79) |
| | Haemoglobin | 6 | 14.52(6.43–32.82) | 14.52(72.81) | 14.03(6.21) | 3.81 (2.13) |
| | Metabolic function test abnormal | 4 | 8.23(3.06–22.17) | 8.23(24.89) | 8.08(3) | 3.01 (1.34) |
| | Platelet count | 4 | 9.06(3.36–24.41) | 9.06(28.01) | 8.87(3.29) | 3.15 (1.47) |
| | Thyroglobulin increased | 4 | 11.16(4.13–30.15) | 11.16(35.94) | 10.87(4.02) | 3.44 (1.76) |
| | International normalised ratio | 3 | 7.75(2.47–24.30) | 7.75(17.29) | 7.62(2.43) | 2.93 (1.25) |
| Skin and subcutaneous tissue disorders | Palmar-plantar erythrodysaesthesia syndrome | 1261 | 27.67 (26.12–29.30) | 27.41 (29960.99) | 25.65(24.22) | 4.68 (3.01) |
| | Blister | 685 | 6.14(5.69–6.62) | 6.11(2885.05) | 6.03(5.59) | 2.59 (0.93) |
| | Yellow skin | 629 | 72.94 (66.98–79.45) | 72.59 (37367.23) | 61.23(56.22) | 5.94 (4.27) |
| | Skin exfoliation | 570 | 3.55(3.27–3.85) | 3.54(1029.46) | 3.51(3.24) | 1.81 (0.15) |
| | Hair colour changes | 429 | 14.95 (13.57–16.46) | 14.9(5357.21) | 14.38(13.06) | 3.85 (2.18) |
| | Skin discolouration | 407 | 4.20(3.81–4.63) | 4.19(977.2) | 4.15(3.77) | 2.05 (0.39) |
| | Hyperkeratosis | 221 | 19.86 (17.35–22.74) | 19.83 (3758.76) | 18.91(16.52) | 4.24 (2.57) |
| | Skin lesion | 185 | 3.34(2.89–3.86) | 3.34(300.57) | 3.32(2.87) | 1.73 (0.06) |
| | Skin fissures | 177 | 5.83(5.02–6.76) | 5.82(696.06) | 5.75(4.95) | 2.52 (0.86) |
| | Decubitus ulcer | 59 | 3.30(2.55–4.26) | 3.3(93.59) | 3.28(2.54) | 1.71 (0.05) |
| | Skin atrophy | 49 | 4.18(3.16–5.54) | 4.18(117.4) | 4.15(3.13) | 2.05 (0.39) |
| | Skin toxicity | 45 | 4.58(3.41–6.15) | 4.58(124.44) | 4.54(3.38) | 2.18 (0.52) |
| | Skin hypertrophy | 37 | 6.43(4.64–8.89) | 6.42(166.66) | 6.33(4.58) | 2.66 (1.00) |
| | Nail discolouration | 35 | 4.25(3.05–5.93) | 4.25(86.07) | 4.22(3.02) | 2.08 (0.41) |
| | Blood blister | 26 | 3.81(2.59–5.61) | 3.81(53.41) | 3.78(2.57) | 1.92 (0.25) |
| | Skin sensitisation | 23 | 10.34(6.84–15.65) | 10.34(189.01) | 10.1(6.67) | 3.34 (1.67) |
| | Plantar erythema | 18 | 34.82 (21.49–56.41) | 34.81(542.14) | 32.01(19.76) | 5.00 (3.32) |
| | Palmar erythema | 14 | 5.75(3.39–9.74) | 5.74(54.06) | 5.67(3.35) | 2.50 (0.84) |
| | Skin depigmentation | 12 | 4.17(2.36–7.36) | 4.17(28.59) | 4.13(2.34) | 2.05 (0.38) |
| | Nail bed bleeding | 8 | 7.51(3.73–15.12) | 7.51(44.28) | 7.39(3.67) | 2.88 (1.21) |
| | Scar pain | 7 | 8.26(3.91–17.47) | 8.26(43.76) | 8.11(3.84) | 3.02 (1.35) |
| | Sweat discolouration | 5 | 14.05(5.75–34.29) | 14.05(58.46) | 13.59(5.57) | 3.76 (2.08) |
| | Splinter haemorrhages | 5 | 16.73(6.84–40.97) | 16.73(70.89) | 16.08(6.57) | 4.01 (2.32) |
| | Nail pigmentation | 4 | 8.06(2.99–21.70) | 8.06(24.23) | 7.92(2.94) | 2.98 (1.31) |
| | Umbilical haemorrhage | 4 | 15.71(5.78–42.70) | 15.71(52.93) | 15.13(5.57) | 3.92 (2.23) |
| Nervous system disorders | Dysgeusia | 1577 | 9.80(9.32–10.31) | 9.7(12013.08) | 9.48(9.02) | 3.25 (1.58) |
| | Ageusia | 595 | 11.50 (10.59–12.47) | 11.45 (5511.42) | 11.15(10.27) | 3.48 (1.81) |

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**Table 3** (*continued*)

| SOC | PT | Reports | ROR, 95%Cl | PRR($\chi^2$) | EBGM (EBGM05) | IC (IC025) |
|---|---|---|---|---|---|---|
| | Taste disorder | 134 | 4.46(3.76–5.28) | 4.45(354.59) | 4.41(3.72) | 2.14 (0.48) |
| | Hyperaesthesia | 127 | 6.89(5.78–8.21) | 6.88(627.55) | 6.78(5.69) | 2.76 (1.10) |
| | Hypogeusia | 60 | 14.25 (11.01–18.44) | 14.25(712.64) | 13.77(10.64) | 3.78 (2.12) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Neoplasm progression | 1689 | 24.34 (23.16–25.57) | 24.03 (35111.09) | 22.68(21.58) | 4.50 (2.84) |
| | Renal cell carcinoma | 893 | 87.33 (81.20–93.92) | 86.73 (61763.31) | 70.96(65.98) | 6.15 (4.48) |
| | Metastatic renal cell carcinoma | 691 | 259.10 (235.27–285.35) | 257.71 (105839.05) | 154.76 (140.52) | 7.27 (5.61) |
| | Renal cancer | 559 | 4.63(4.26–5.03) | 4.61(1563.66) | 4.57(4.2) | 2.19 (0.53) |
| | Neoplasm malignant | 456 | 3.34(3.04–3.66) | 3.33(736.89) | 3.31(3.02) | 1.73 (0.06) |
| | Gastrointestinal stromal tumour | 292 | 53.48 (47.32–60.46) | 53.37 (13177.83) | 46.99(41.57) | 5.55 (3.89) |
| | Second primary malignancy | 232 | 13.17 (11.56–15.02) | 13.15 (2518.95) | 12.75(11.18) | 3.67 (2.01) |
| | Renal cancer metastatic | 165 | 117.32 (98.55–139.67) | 117.17 (14569.57) | 90.06(75.65) | 6.49 (4.82) |
| | Renal cancer stage IV | 47 | 6.37(4.78–8.50) | 6.37(209.4) | 6.28(4.71) | 2.65 (0.99) |
| | Tumour haemorrhage | 45 | 7.81(5.81–10.49) | 7.81(261.71) | 7.67(5.71) | 2.94 (1.27) |
| | Pancreatic neuroendocrine tumour | 45 | 39.11 (28.78–53.15) | 39.1(1516.5) | 35.58(26.19) | 5.15 (3.48) |
| | Tumour pain | 44 | 16.54 (12.23–22.37) | 16.54(615.89) | 15.9(11.76) | 3.99 (2.32) |
| | Cancer pain | 41 | 7.74(5.68–10.54) | 7.74(235.73) | 7.6(5.58) | 2.93 (1.26) |
| | Neoplasm recurrence | 32 | 4.69(3.31–6.65) | 4.69(91.74) | 4.64(3.28) | 2.22 (0.55) |
| | Tumour rupture | 29 | 29.77 (20.40–43.44) | 29.76(748.29) | 27.7(18.98) | 4.79 (3.12) |
| | Renal cell carcinoma stage IV | 25 | 106.93 (68.65–166.56) | 106.91 (2052.85) | 83.89(53.86) | 6.39 (4.70) |
| | Malignant pleural effusion | 17 | 4.75(2.95–7.67) | 4.75(49.74) | 4.71(2.92) | 2.23 (0.57) |
| | Soft tissue sarcoma | 17 | 21.39 (13.12–34.85) | 21.38(312.92) | 20.31(12.46) | 4.34 (2.67) |
| | Tumour necrosis | 16 | 7.19(4.39–11.80) | 7.19(83.77) | 7.08(4.32) | 2.82 (1.16) |
| | Malignant urinary tract neoplasm | 16 | 75.11 (43.96–128.34) | 75.1(978.83) | 63(36.87) | 5.98 (4.29) |
| | Clear cell renal cell carcinoma | 15 | 10.65(6.38–17.79) | 10.65(127.66) | 10.39(6.22) | 3.38 (1.71) |
| | Pancreatic neuroendocrine tumour metastatic | 14 | 31.89 (18.49–55.00) | 31.88(386.78) | 29.52(17.12) | 4.88 (3.20) |
| | Neuroendocrine tumour | 13 | 4.39(2.54–7.59) | 4.39(33.68) | 4.35(2.52) | 2.12 (0.45) |
| | Carcinoid tumour | 13 | 7.26(4.20–12.57) | 7.26(68.9) | 7.15(4.13) | 2.84 (1.17) |
| | Neuroendocrine carcinoma | 11 | 7.70(4.24–13.98) | 7.7(62.85) | 7.57(4.17) | 2.92 (1.25) |
| | Thyroid cancer metastatic | 8 | 14.13(6.98–28.60) | 14.12(94.11) | 13.66(6.75) | 3.77 (2.09) |
| | Intracranial tumour haemorrhage | 6 | 7.29(3.25–16.34) | 7.28(31.93) | 7.17(3.2) | 2.84 (1.17) |
| | Tumour compression | 6 | 8.88(3.95–19.95) | 8.88(41.02) | 8.7(3.87) | 3.12 (1.45) |
| | Connective tissue neoplasm | 6 | 100.41 (40.88–246.60) | 100.41 (468.33) | 79.84(32.51) | 6.32 (4.57) |
| | Paraganglion neoplasm | 4 | 11.16(4.13–30.15) | 11.16(35.94) | 10.87(4.02) | 3.44 (1.76) |
| | Malignant neoplasm of renal pelvis | 4 | 13.05(4.82–35.34) | 13.05(43.04) | 12.65(4.67) | 3.66 (1.98) |

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**Table 3** (*continued*)

| SOC | PT | Reports | ROR, 95%Cl | PRR($\chi^2$) | EBGM (EBGM05) | IC (IC025) |
|---|---|---|---|---|---|---|
| | Spindle cell sarcoma | 4 | 13.05(4.82–35.34) | 13.05(43.04) | 12.65(4.67) | 3.66 (1.98) |
| | Thymoma malignant | 4 | 26.10(9.48–71.84) | 26.09(90.4) | 24.5(8.9) | 4.61 (2.91) |
| | Alveolar soft part sarcoma | 4 | 46.65 (16.53–131.69) | 46.65(159.38) | 41.72(14.78) | 5.38 (3.65) |
| | Sarcoma metastatic | 3 | 9.79(3.11–30.78) | 9.79(23.08) | 9.57(3.04) | 3.26 (1.57) |
| | Chordoma | 3 | 14.08(4.45–44.57) | 14.08(35.17) | 13.62(4.3) | 3.77 (2.07) |
| | Thymic cancer metastatic | 3 | 31.21 (9.62–101.22) | 31.21(81.14) | 28.94(8.92) | 4.86 (3.13) |
| | Haemangiopericytoma | 3 | 72.17 (21.03–247.68) | 72.17(177.3) | 60.93(17.75) | 5.93 (4.14) |
| Respiratory, thoracic and mediastinal disorders | Epistaxis | 637 | 4.01(3.71–4.34) | 3.99(1416.75) | 3.96(3.66) | 1.99 (0.32) |
| | Pleural effusion | 477 | 3.66(3.34–4.00) | 3.65(909.49) | 3.62(3.31) | 1.86 (0.19) |
| | Hiccups | 88 | 5.33(4.32–6.57) | 5.32(304.78) | 5.26(4.27) | 2.40 (0.73) |
| | Nasal discomfort | 58 | 3.37(2.61–4.37) | 3.37(96.04) | 3.35(2.59) | 1.75 (0.08) |
| | Nasal disorder | 25 | 4.32(2.91–6.41) | 4.32(63.14) | 4.29(2.89) | 2.10 (0.43) |
| | Hydrothorax | 23 | 13.04(8.61–19.76) | 13.04(247.26) | 12.64(8.34) | 3.66 (1.99) |
| | Oropharyngeal blistering | 18 | 4.71(2.96–7.50) | 4.71(51.96) | 4.66(2.93) | 2.22 (0.55) |
| | Throat lesion | 15 | 9.89(5.92–16.51) | 9.89(116.81) | 9.66(5.79) | 3.27 (1.60) |
| | Pharyngeal inflammation | 12 | 4.88(2.76–8.62) | 4.88(36.52) | 4.83(2.73) | 2.27 (0.60) |
| | Oropharyngeal plaque | 5 | 5.30(2.19–12.81) | 5.3(17.21) | 5.24(2.17) | 2.39 (0.72) |
| | Oesophagobronchial fistula | 3 | 9.46(3.01–29.76) | 9.46(22.17) | 9.26(2.95) | 3.21 (1.53) |
| Metabolism and nutrition disorders | Decreased appetite | 2108 | 4.28(4.10–4.47) | 4.22(5150.11) | 4.19(4.01) | 2.07 (0.40) |
| | Feeding disorder | 180 | 5.22(4.50–6.05) | 5.21(604.9) | 5.16(4.45) | 2.37 (0.70) |
| | Appetite disorder | 50 | 3.99(3.02–5.27) | 3.99(110.86) | 3.96(3) | 1.99 (0.32) |
| | Fluid intake reduced | 38 | 3.90(2.83–5.37) | 3.9(81.14) | 3.87(2.81) | 1.95 (0.29) |
| Musculoskeletal and connective tissue disorders | Mastication disorder | 24 | 3.84(2.57–5.75) | 3.84(49.97) | 3.81(2.55) | 1.93 (0.26) |
| | Degenerative bone disease | 6 | 7.17(3.20–16.08) | 7.17(31.29) | 7.06(3.15) | 2.82 (1.15) |
| | Bone fistula | 3 | 7.45(2.38–23.35) | 7.45(16.43) | 7.33(2.34) | 2.87 (1.19) |
| | Jaw fistula | 3 | 12.28(3.89–38.78) | 12.28(30.13) | 11.93(3.78) | 3.58 (1.89) |
| Injury, poisoning and procedural complications | Mouth injury | 77 | 25.28 (20.07–31.84) | 25.27(1684) | 23.77(18.87) | 4.57 (2.90) |
| | Tongue injury | 19 | 9.83(6.23–15.50) | 9.83(146.94) | 9.61(6.09) | 3.26 (1.60) |
| | Anal injury | 15 | 44.76 (26.22–76.40) | 44.75(574.82) | 40.2(23.55) | 5.33 (3.65) |
| | Skin wound | 11 | 4.01(2.21–7.26) | 4.01(24.59) | 3.98(2.2) | 1.99 (0.32) |
| | Incision site pain | 10 | 3.88(2.08–7.23) | 3.88(21.16) | 3.85(2.07) | 1.95 (0.28) |
| | Burn oral cavity | 10 | 8.50(4.54–15.90) | 8.5(64.71) | 8.33(4.45) | 3.06 (1.39) |
| | Burn oesophageal | 7 | 5.87(2.78–12.38) | 5.87(27.86) | 5.8(2.75) | 2.54 (0.86) |
| | Ear injury | 5 | 5.08(2.10–12.27) | 5.08(16.16) | 5.02(2.08) | 2.33 (0.66) |

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**Table 3** (*continued*)

| SOC | PT | Reports | ROR, 95%Cl | PRR($\chi^2$) | EBGM (EBGM05) | IC (IC025) |
|---|---|---|---|---|---|---|
| | Penis injury | 5 | 5.96(2.46–14.41) | 5.96(20.32) | 5.88(2.43) | 2.56 (0.88) |
| | Gingival injury | 4 | 8.19(3.04–22.05) | 8.19(24.72) | 8.04(2.99) | 3.01 (1.33) |
| | Genital injury | 4 | 15.87(5.84–43.15) | 15.87(53.53) | 15.28(5.62) | 3.93 (2.24) |
| | Vena cava injury | 3 | 13.43(4.25–42.45) | 13.43(33.34) | 13.01(4.11) | 3.70 (2.01) |
| Infections and infestations | Anal abscess | 39 | 3.53(2.58–4.84) | 3.53(70.21) | 3.51(2.56) | 1.81 (0.15) |
| | Dysentery | 32 | 8.28(5.84–11.76) | 8.28(200.6) | 8.13(5.73) | 3.02 (1.36) |
| | Cholecystitis infective | 22 | 3.87(2.54–5.89) | 3.87(46.4) | 3.84(2.53) | 1.94 (0.28) |
| | Hand-foot-and-mouth disease | 12 | 10.02(5.65–17.77) | 10.02(94.95) | 9.79(5.52) | 3.29 (1.62) |
| | Blister infected | 8 | 4.97(2.47–9.98) | 4.97(25.02) | 4.92(2.45) | 2.30 (0.63) |
| | Anal infection | 5 | 9.82(4.04–23.85) | 9.82(38.62) | 9.6(3.95) | 3.26 (1.58) |
| | Upper respiratory tract infection bacterial | 3 | 6.83(2.18–21.40) | 6.83(14.68) | 6.73(2.15) | 2.75 (1.07) |
| | Arteriovenous fistula site infection | 3 | 9.31(2.96–29.27) | 9.31(21.73) | 9.12(2.9) | 3.19 (1.50) |
| Vascular disorders | Hypertension | 1496 | 3.40(3.23–3.57) | 3.37(2477.03) | 3.35(3.18) | 1.74 (0.08) |
| | Aortic dissection | 31 | 3.30(2.32–4.70) | 3.3(49.22) | 3.28(2.3) | 1.71 (0.05) |
| | Vena cava thrombosis | 18 | 4.96(3.12–7.90) | 4.96(56.23) | 4.91(3.09) | 2.30 (0.63) |
| | Capillary fragility | 6 | 5.61(2.50–12.55) | 5.61(22.38) | 5.54(2.47) | 2.47 (0.80) |
| | Capillary disorder | 5 | 6.27(2.59–15.17) | 6.27(21.79) | 6.18(2.56) | 2.63 (0.95) |
| Blood and lymphatic system disorders | Thrombocytopenia | 746 | 3.28(3.05–3.53) | 3.27(1165.57) | 3.25(3.02) | 1.70 (0.03) |
| | Bone marrow failure | 236 | 4.92(4.33–5.60) | 4.91(726.95) | 4.87(4.28) | 2.28 (0.62) |
| Psychiatric disorders | Eating disorder | 240 | 5.26(4.63–5.98) | 5.25(815.57) | 5.2(4.57) | 2.38 (0.71) |
| | Mutism | 15 | 4.84(2.91–8.05) | 4.84(45.12) | 4.79(2.88) | 2.26 (0.59) |
| Renal and urinary disorders | Chromaturia | 206 | 4.11(3.58–4.72) | 4.11(479.01) | 4.07(3.55) | 2.03 (0.36) |
| | Proteinuria | 120 | 3.25(2.72–3.90) | 3.25(185.67) | 3.23(2.7) | 1.69 (0.03) |
| | Nephrotic syndrome | 53 | 3.75(2.86–4.92) | 3.75(105.92) | 3.72(2.84) | 1.90 (0.23) |
| | Renal haemorrhage | 20 | 4.43(2.85–6.88) | 4.43(52.5) | 4.39(2.83) | 2.13 (0.47) |
| | Haemorrhage urinary tract | 19 | 3.49(2.22–5.48) | 3.49(33.41) | 3.46(2.21) | 1.79 (0.13) |
| | Renal vascular thrombosis | 3 | 8.81(2.81–27.69) | 8.81(20.32) | 8.64(2.75) | 3.11 (1.43) |
| Cardiac disorders | Cardiopulmonary failure | 160 | 18.78 (16.02–22.01) | 18.76 (2564.99) | 17.93(15.3) | 4.16 (2.50) |
| Eye disorders | Eyelid oedema | 89 | 3.27(2.66–4.03) | 3.27(139.11) | 3.25(2.64) | 1.70 (0.03) |
| | Periorbital oedema | 72 | 6.66(5.28–8.41) | 6.66(340.25) | 6.56(5.2) | 2.71 (1.05) |
| | Eyelash discolouration | 29 | 68.92 (46.42–102.32) | 68.9(1645.9) | 58.59(39.46) | 5.87 (4.19) |
| | Eye oedema | 26 | 5.04(3.42–7.42) | 5.04(83.15) | 4.99(3.39) | 2.32 (0.65) |
| | Eye colour change | 9 | 4.34(2.25–8.36) | 4.34(22.84) | 4.3(2.23) | 2.10 (0.43) |
| | Orbital oedema | 8 | 7.14(3.55–14.38) | 7.14(41.5) | 7.03(3.49) | 2.81 (1.14) |

(*continued on next page*)

**Table 3** (*continued*)

| SOC | PT | Reports | ROR, 95%Cl | PRR($\chi^2$) | EBGM (EBGM05) | IC (IC025) |
|---|---|---|---|---|---|---|
| | Lacrimal disorder | 7 | 5.41(2.57–11.41) | 5.41(24.82) | 5.35(2.54) | 2.42 (0.75) |
| | Scleral haemorrhage | 4 | 7.58(2.82–20.40) | 7.58(22.42) | 7.46(2.77) | 2.90 (1.22) |
| Hepatobiliary disorders | Jaundice | 226 | 3.76(3.30–4.29) | 3.75(452.45) | 3.73(3.27) | 1.90 (0.23) |
| | Hepatic haemorrhage | 10 | 5.64(3.02–10.52) | 5.64(37.58) | 5.57(2.98) | 2.48 (0.81) |
| | Hydrocholecystis | 3 | 7.50(2.39–23.51) | 7.5(16.57) | 7.37(2.35) | 2.88 (1.20) |
| | Perihepatic discomfort | 3 | 17.76(5.58–56.52) | 17.76(45.37) | 17.02(5.35) | 4.09 (2.39) |
| Endocrine disorders | Hypothyroidism | 473 | 7.51(6.86–8.23) | 7.49(2608.4) | 7.36(6.72) | 2.88 (1.21) |
| | Thyroid disorderF | 200 | 6.32(5.50–7.27) | 6.31(880.22) | 6.23(5.42) | 2.64 (0.97) |
| | Carcinoid syndrome | 7 | 8.81(4.16–18.63) | 8.8(47.35) | 8.63(4.08) | 3.11 (1.44) |
| | Myxoedema | 7 | 18.84(8.82–40.24) | 18.84(112.74) | 18.01(8.43) | 4.17 (2.49) |
| | Central hypothyroidism | 6 | 10.89(4.84–24.52) | 10.89(52.43) | 10.62(4.72) | 3.41 (1.73) |
| | Primary hypothyroidism | 4 | 11.32(4.19–30.60) | 11.32(36.56) | 11.03(4.08) | 3.46 (1.78) |
| | Thyroid atrophy | 3 | 19.57(6.14–62.43) | 19.57(50.31) | 18.67(5.85) | 4.22 (2.52) |
| Reproductive system and breast disorders | Genital rash | 26 | 8.64(5.86–12.75) | 8.64(171.84) | 8.47(5.74) | 3.08 (1.42) |
| | Pruritus genital | 17 | 3.69(2.29–5.95) | 3.69(33.03) | 3.66(2.27) | 1.87 (0.21) |
| | Genital erythema | 13 | 14.94(8.58–26.00) | 14.94(162.73) | 14.42(8.28) | 3.85 (2.18) |
| | Testicular swelling | 11 | 4.02(2.22–7.28) | 4.02(24.71) | 3.99(2.2) | 2.00 (0.33) |
| | Penile haemorrhage | 10 | 5.49(2.94–10.25) | 5.49(36.21) | 5.43(2.91) | 2.44 (0.77) |
| | Genital lesion | 10 | 11.29(6.02–21.17) | 11.29(91.09) | 10.99(5.86) | 3.46 (1.79) |
| | Genital burning sensation | 8 | 4.62(2.30–9.27) | 4.62(22.4) | 4.57(2.28) | 2.19 (0.52) |
| | Perineal pain | 6 | 4.61(2.06–10.31) | 4.61(16.76) | 4.57(2.04) | 2.19 (0.52) |
| | Genital discomfort | 6 | 5.21(2.33–11.67) | 5.21(20.16) | 5.16(2.3) | 2.37 (0.69) |
| | Penile erythema | 5 | 6.29(2.60–15.22) | 6.29(21.88) | 6.2(2.56) | 2.63 (0.96) |
| | Scrotal ulcer | 5 | 8.33(3.44–20.21) | 8.33(31.57) | 8.18(3.37) | 3.03 (1.35) |
| | Scrotal disorder | 4 | 5.62(2.09–15.08) | 5.62(14.97) | 5.55(2.07) | 2.47 (0.80) |
| | Vaginal lesion | 4 | 5.79(2.16–15.54) | 5.79(15.61) | 5.72(2.13) | 2.52 (0.84) |
| | Vaginal mucosal blistering | 4 | 7.70(2.86–20.71) | 7.7(22.85) | 7.57(2.81) | 2.92 (1.24) |
| | Scrotal erythema | 4 | 11.40(4.22–30.83) | 11.4(36.87) | 11.1(4.11) | 3.47 (1.79) |
| | Penile exfoliation | 4 | 26.10(9.48–71.84) | 26.09(90.4) | 24.5(8.9) | 4.61 (2.91) |
| | Scrotal inflammation | 4 | 41.61 (14.83–116.75) | 41.61(143.07) | 37.65(13.42) | 5.23 (3.51) |
| | Genital blister | 3 | 6.41(2.05–20.08) | 6.41(13.49) | 6.33(2.02) | 2.66 (0.98) |
| Surgical and medical procedures | Nephrectomy | 16 | 5.16(3.15–8.45) | 5.16(52.98) | 5.11(3.12) | 2.35 (0.68) |
| Immune system disorders | Decreased immune responsiveness | 58 | 3.24(2.50–4.19) | 3.24(88.84) | 3.22(2.48) | 1.69 (0.02) |
| Social circumstances | Walking disability | 16 | 3.48(2.13–5.70) | 3.48(28.07) | 3.46(2.12) | 1.79 (0.12) |

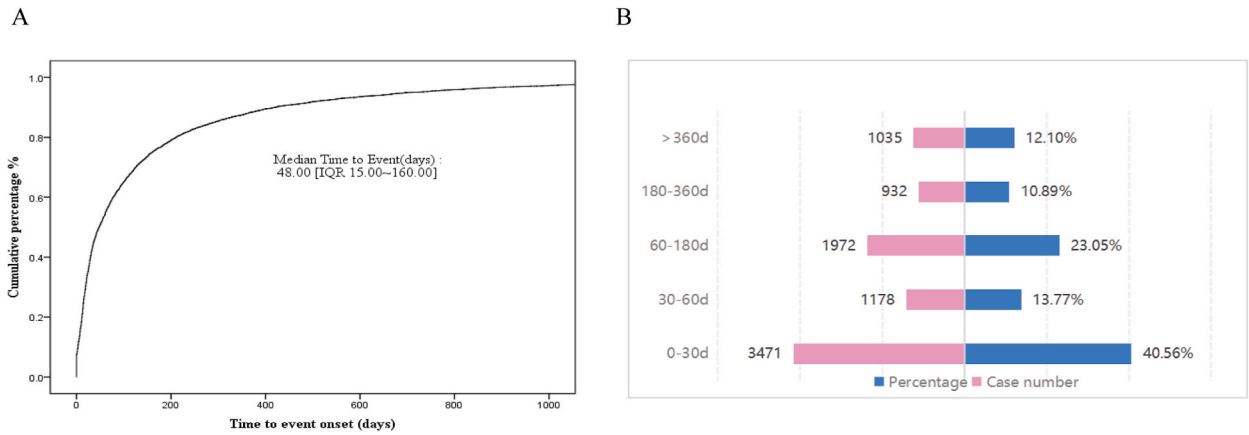


**Fig. 2.** Time to onset of sunitinib-related AEs. A.Cumulative percentage curve for time to onset of sunitinib-related AEs. B.Distribution of sunitinib-related AEs across the time to onset.

limit of the ROR value exceeded 1, indicating the presence of positive signals. This information is visually represented in Fig. 3. The signal intensity of the 237 sunitinib-related AEs across different time periods is detailed in Table S3.

## 4. Discussion

Sunitinib has been used in clinical practice for 17 years since its introduction in 2006. Despite its generally recognized safety, there have been reported cases of AEs. To better understand its safety, we analyzed FDA AEs data from Q1 2006 to Q1 2023. The data indicated that there were a total of 31,530 AE reports associated with sunitinib, with an average of approximately 2000 cases per year. Among these reports, 60.16 % pertained to male patients, a proportion significantly greater than the 31.95 % attributed to female patients. The median age of patients affected was 65 years, aligning with the typical age range of individuals diagnosed with advanced renal clear cell carcinoma, the primary indication for sunitinib therapy. Renal cell carcinoma is estimated to comprise 2 %–3 % of adult malignancies worldwide, with a higher incidence observed in the elderly demographic [19]. Based on the GLOBOCAN2020 global cancer statistics [20], the age-standardized incidence rates of renal cell carcinoma are 6.1 per 100,000 in men and 3.2 per 100,000 in women. Among these cases, 16,654 instances, representing 52.82 % of the total, were reported in the United States. This phenomenon is associated with variations in the prevalence of renal clear cell carcinoma across various regions, as well as disparities in the timing of pharmaceutical product introductions in diverse nations and the presence of geographic information asymmetry within the FAERS

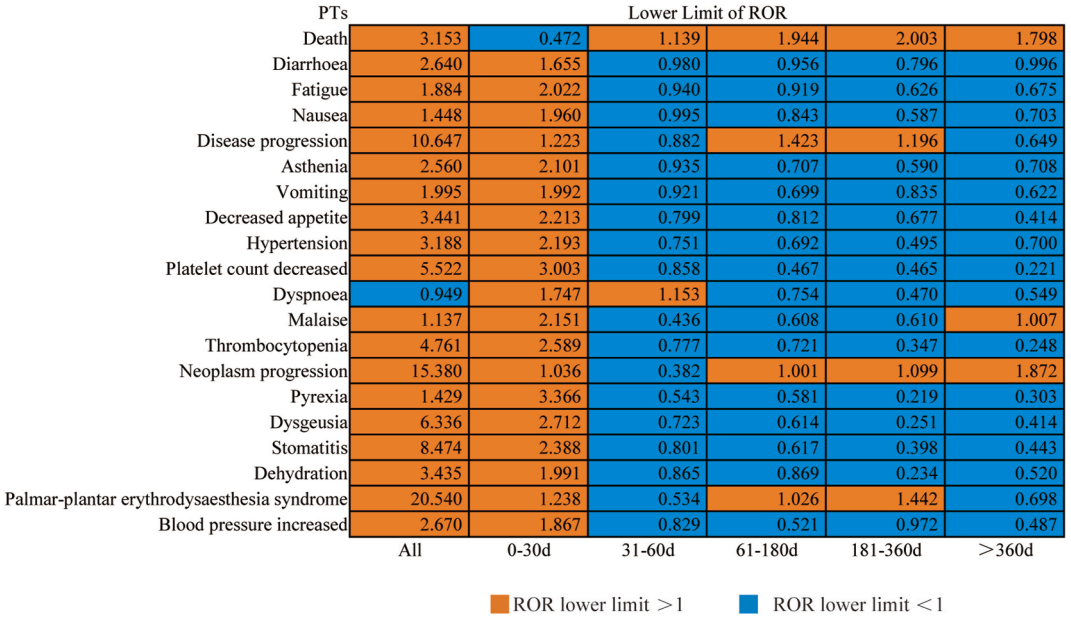


**Fig. 3.** Top 20 sunitinib-related AEs in different Time Periods.

database. Based on existing research [20], the prevalence of renal clear cell carcinoma is most pronounced in industrialized Western nations, notably North America and Western Europe, while it is notably lower in developing regions like Africa and Asia. This variance across geographical regions may be attributed to a range of factors including lifestyle practices, environmental influences, and genetic predispositions unique to each locale. Furthermore, variations in the marketing timelines of pharmaceuticals across countries, coupled with the predominance of reports in the FAERS database from Europe and the United States [21], may result in a limited number of adverse event reports from other global regions.

Our comprehensive analysis focused on the SOC level implicated in the primary adverse effects of sunitinib, revealing that Gastrointestinal and Endocrine disorders exhibited the most pronounced signals. Additionally, the presence of positive signals encompassing the vast majority of AEs in the insert of sunitinib further bolstered the credibility of our study methodologies and findings. Significantly, this study identified new AE signals for Pleural effusion (n = 477, ROR 3.66; 95%CI 3.34–4.00) and Ascites (n = 319, ROR 5.07, 95%CI 4.54–5.67). While previous reports of sunitinib-induced pleural effusions and ascites have been limited, a study documented a case of pericardial and pleural effusion combined with ascites in the context of severe hypothyroidism linked to sunitinib use [22]. This literature posits that pleural effusion and ascites may arise as secondary effects of severe hypothyroidism induced by sunitinib. As such, vigilant monitoring of thyroid function and prompt initiation of levothyroxine replacement therapy following the onset of hypothyroidism are recommended. Additionally, close observation for the emergence of pleural or abdominal effusions during sunitinib treatment is advised. Timely intervention can help mitigate the progression of these complications. In addition, pleural or abdominal effusion may be linked to additional factors, including hypoalbuminemia and tumor metastasis to the thoracic and abdominal cavities, necessitating additional clinical observation and research for clarification.

The mention of potential adrenal toxicity in the sunitinib insert is supported by preclinical studies in rats and monkeys demonstrating adrenal toxicity, including cortical congestion, haemorrhage, or necrosis [23]. Nevertheless, our study did not detect any indications of adrenal-related AEs, and prior research has indicated that patients taking sunitinib did not experience significant adrenal insufficiency [23]. The incidence of adrenal gland impairment in patients receiving sunitinib is relatively low; however, due to the potential for subclinical adrenal insufficiency to be obscured by physiological stress, it is imperative to conduct screening for adrenal insufficiency in patients undergoing surgery, experiencing trauma, or suffering from severe infections as deemed appropriate.

This study identified an early occurrence of sunitinib-related AEs, occurring at a median of 48 days. The majority of these AEs manifested within the initial month following the commencement of treatment (n = 3471, 40.56 %), consistent with findings from previous phase II/III clinical trials [24–28]. Through a comprehensive analysis of the occurrence of AEs across various time intervals, it was determined that the initial month exhibited a heightened frequency of AEs, with dyspnoea emerging as a predominant issue in the subsequent month. The precise etiology of sunitinib-induced dyspnoea remains unclear at present. Existing research suggests a potential link between sunitinib administration and the development of interstitial pneumonitis, particularly in individuals with a history of radiotherapy [29–31]. Symptoms in this cohort of patients may be alleviated through dose reduction of sunitinib and administration of prednisolone pulse therapy [31]. Palmar-Plantar Erythrodysesthesia syndrome is linked to cutaneous and vascular injury caused by sunitinib. Literature has indicated that this adverse reaction typically manifests within the initial days to three weeks of treatment [32–34]. Our study further found that such AEs may still occur after six months of dosing in addition to the first month. In patients receiving sunitinib treatment for a duration exceeding one year, the primary adverse outcomes observed were tumor progression and mortality, potentially attributable to the development of tumor resistance. Prolonged administration of sunitinib does not appear to induce novel categories of treatment-associated AEs.

This study is subject to several limitations. Firstly, the database report relied on voluntary submissions, with 42.69 % of AE cases originating from spontaneous reporting by consumers, potentially introducing bias. Secondly, while a large number of case reports were obtained, the lack of details on drug exposure in patients without adverse events hinders the accurate calculation of adverse event incidence. Furthermore, it is crucial to clarify that the present analyses do not permit direct inference of precise causality. Although the discretisation analysis offers an approximation of signal strength that is statistically significant, it does not quantify risk or establish a direct causal connection. Consequently, to validate the precise relationship, it remains imperative to depend on the findings of prospective clinical studies.

## 5. Conclusion

In the clinical utilization of sunitinib, vigilant monitoring of potential adverse reactions is imperative during the initial phase of drug administration. In addition to the documented adverse reactions outlined in the drug specification, healthcare providers should remain attentive to potential adverse reactions such as pleural effusion, ascites, and tumor development. The early detection of these events is vital for timely intervention and management, thereby optimizing patient safety and treatment outcomes.

## Data and code availability

The raw data for this study are available from the FDA Adverse Event Reporting System website https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html, and the datasets generated and analyzed in the study are available from the corresponding author upon request.

## CRediT authorship contribution statement

**Wenbin Zou:** Writing – original draft. **Han Yang:** Writing – original draft, Conceptualization. **Yu Xi:** Data curation. **Chenxi Zeng:**

Data curation. **Wei Chen:** Writing – review & editing. **Xiangning Fu:** Conceptualization.

## 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.e37543.

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