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# Characterization of adverse reactions to four common targeted drugs for hepatocellular carcinoma in WHO-VigiAccess

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**Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality, with limited therapeutic options available for advanced stages of the disease. Treatment strategies for HCC are multimodal and largely depend on the disease stage, liver function, and individual patient factors. Based on the WHO's VigiAccess database, this study employed a retrospective descriptive analysis of adverse drug reaction (ADR) reports associated with four widely used tyrosine kinase inhibitors (TKIs) for HCC, including Sorafenib, Cabozantinib, Lenvatinib, and Regorafenib. The analysis included demographic data such as patient age, gender, and geographical distribution, alongside clinical information on the systems and symptoms associated with ADR reports. A total of 112,975 ADR reports related to the four TKI-targeted drugs were identified. Sorafenib exhibited the highest ADR reporting rate (30.7%), followed by Cabozantinib (29.4%), Lenvatinib (24.5%), and Regorafenib (15.4%). The odds ratio method was employed to assess the statistical correlation between the use of these targeted drugs and the occurrence of ADRs. Notably, Sorafenib (3,746) and Regorafenib (2,496) served to have the highest number of reported palmar-plantar erythrodysaesthesia syndrome. Chi-square analyses suggested that ADRs related to Lenvatinib were reported significantly more frequently in female patients compared to their male counterparts. The findings of this study can enhance public awareness of drug-related adverse events and provide an evidence-based foundation for prioritizing the management of ADRs associated with TKIs in second-line HCC therapy.**

**Keywords** Hepatocellular carcinoma, Tyrosine kinase inhibitor, VigiAccess, Adverse drug reaction, Adverse event

Hepatocellular carcinoma (HCC) represents a leading cause of cancer-related mortality globally. However, treatment options for advanced stages of the disease remain limited. The management of HCC is multimodal, influenced by the disease stage, liver function, and individual patient characteristics[1,2]. Surgical resection, liver transplantation, and local ablative therapies (such as radiofrequency ablation and microwave ablation), are typically employed for early-stage HCC. For intermediate-stage HCC, trans-arterial chemoembolization (TACE) and trans-arterial radioembolization (TARE) are commonly adopted. Systemic therapies, including targeted therapies and immunotherapy, are generally reserved for advanced HCC[3–5].

Although the combination of atezolizumab and bevacizumab (IMbrave150 regimen) has emerged as the first-line standard of care for unresectable HCC[6], tyrosine kinase inhibitors (TKIs) remain a critical treatment option for second-line therapy or for patients with specific molecular subtypes[7]. Sorafenib, one of the first approved targeted therapies for HCC, works by inhibiting tumor angiogenesis and cell proliferation through the blockade of multiple kinases, including vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR). It was the first systemic treatment to significantly improve overall survival in advanced HCC patients[8]. However, Sorafenib is also associated with adverse effects, such as hand and foot skin reactions, diarrhea, and hypertension. Following Sorafenib, several TKIs have been evaluated in clinical trials. Regorafenib, a multikinase inhibitor with a similar target profile to Sorafenib, has been approved for advanced HCC patients who have progressed on Sorafenib therapy[9]. Adverse effects of Regorafenib may include fatigue, anorexia, and hypertension. Lenvatinib, which targets multiple receptors including VEGFR-1, VEGFR-2, VEGFR-3, FGFR-1, FGFR-2, FGFR-3, PDGFR-α, and RET, has demonstrated non-inferiority to Sorafenib in a phase 3 trial[10]. Its

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typical adverse reactions include hypertension, proteinuria, and diarrhea. Cabozantinib, which targets MET, VEGFR-2, RET, AXL, and c-KIT, particularly in patients with high c-MET expression[11]. Adverse effects of Cabozantinib may include fatigue, diarrhea, and hypertension.

Long-term use of these TKIs has been implicated in the development of secondary malignancies, particularly in patients with a history of other cancers[12]. A retrospective analysis of patients treated with Sorafenib and Lenvatinib revealed an increased risk of secondary malignancies, with a higher incidence observed in patients with a prior cancer history[13]. This highlights the importance of closely monitoring patients for the emergence of new malignancies during treatment. Despite these potential side effects, TKIs have significantly improved the prognosis for patients with advanced HCC. Specifically, Sorafenib has been shown to extend overall survival by approximately 2.8 months compared to placebo[8]. Regorafenib has similarly demonstrated improved overall survival in patients who have progressed on Sorafenib, with a median overall survival of 10.6 months compared to 7.8 months with placebo[9]. Additionally, Lenvatinib and Cabozantinib have shown improvements in both overall survival and progression-free survival in clinical trials[10,11].

Traditional pharmacovigilance relies heavily on spontaneous reporting systems (SRSs) to detect potential risks through the collection of post-marketing ADR reports[14]. The SRS primarily identifies and accesses potential drug-related risks, encompassing both recognized and previously unreported ADRs, and provides crucial data for ongoing drug safety monitoring. However, traditional SRS is hindered by underreporting, reporting bias, and regional discrepancies. For instance, the likelihood of reporting serious adverse events is 7.2 times higher than that for mild events, resulting in insufficient signal sensitivity. Furthermore, high-income countries contribute over 70% of ADR reports, while low- and middle-income regions suffer from limited data representativeness due to inadequate medical resources and weak surveillance systems[15]. The integration of multidimensional data (e.g., demographics and drug class) and advanced algorithms (e.g., ROR and EBGM) enables more efficient identification of potential ADR signals, thereby enhancing the detection of rare or delayed events[15]. For example, this study identified a high signal for hand-foot skin reactions (ROR = 1.7) using VigiAccess, which might be underestimated in traditional SRS due to underreporting.

Although these drugs provide new therapeutic options for patients with HCC, their use is frequently associated with potential adverse reactions. Clinicians must carefully assess the benefits and risks for each patient and make treatment decisions accordingly. In order to compare the incidence of adverse reactions related to these four TKI drugs, this study conducted a descriptive analysis of spontaneously reported adverse reactions in the VigiAccess database, comparing the reporting rates of these four drugs.

## Methods

### Drug sample

This study compiled data on the currently available TKI-targeted agents for HCC treatment, including their trade names, chemical structures, primary indications, and analogs (Table 1).

### Data sources

From the VigiAccess database (https://www.vigiaccess.org), this study searched for adverse events following the use of each drug between January 1, 2004 and October 28, 2024, based on the drug's generic and trade names. This study focused on four TKI-targeted drugs extensively used for the treatment of HCC. Relevant demographic information, including age group, gender, year of reporting, and geographic distribution by continent, was extracted from the WTO's VigiAccess database. Descriptive data analysis was performed using Excel 2019 software. The VigiAccess database is a publicly accessible resource containing individual case safety reports (ICSRs), which allow users to search for medicine safety reports included in the Uppsala Monitoring Center (UMC). These reports are categorized according to the system organ classification (SOC) and preferred terminology (PT) in the Medical Dictionary for Regulatory Activities (MedDRA). The ADR terms were classified based on MedDRA v25.0. Their plausibility was maintained through quality control measures, including de-

| Drug name | Brand name | Structure | Main conditions | First marketing time | Biosimilars |
|---|---|---|---|---|---|
| Sorafenib | Nexavar | Multi-kinase inhibitor that inhibits the activity of various kinases such as RAF kinase, VEGFR – 2, VEGFR – 3, PDGFR - β, KIT and FLT – 3. | for the treatment of inoperable advanced renal cell carcinoma, inoperable or distant metastatic hepatocellular carcinoma. | 2005 | Regorafenib; Lenvatinib |
| Regorafenib | Stivarga | Multi-kinase inhibitor that acts on multiple targets related to tumor angiogenesis, tumor microenvironment and tumor cell proliferation. | for the treatment of patients with hepatocellular carcinoma, metastatic colorectal cancer, and gastrointestinal mesenchymal stromal tumors previously treated with sorafenib. | 2012 | Sorafenib; Lenvatinib |
| Lenvatinib | Lenvima | Multi-target tyrosine kinase inhibitor, mainly acting on the targets of VEGFR1-3, FGFR1-4, PDGFRα, RET and KIT. | For the treatment of unresectable hepatocellular carcinoma, differentiated thyroid cancer, renal cell carcinoma. | 2015 | Sorafenib; Regorafenib |
| Cabozantinib | Cometriq、Cabometyx | Multi-targeted tyrosine kinase inhibitor that inhibits multiple receptor tyrosine kinase activities, including MET, VEGFR2, and RET. | Cometriq is prescribed for the treatment of medullary thyroid carcinoma and Cabometyx for advanced renal cell carcinoma and HCC. | 2012 (Cometriq); 2016 (Cabometyx); and approved for HCC treatment in 2019 | Sunitinib; Pazopanib |

**Table 1**. General information of four common targeted drugs.

duplication (removal of duplicate report IDs), logical verification (exclusion of non-drug-related ADRs), and expert review (a validation process involving a 20% random sample validated by two independent pharmacists). Safety data were collected for the four TKI-targeted drugs, identifying all ICSRs based on the SOC and PT frameworks in MedDRA[16]. MedDRA terminology, derived from multiple dictionaries, including the WHO Adverse Reaction Terminology (WHO-ART), comprises 27 items within the SOC framework. This analysis selected 20 items closely associated with the symptoms of HCC[17]. This study specifically focused on PT terms, which represent the publicly accessible data level in the VigiBase database via WHO VigiAccess. The reported safety signals were categorized into three levels of severity using outcome codes: fatal, requiring hospitalization, and significant events. Significant events encompass but are not limited to life-threatening incidents, those leading to disability, and congenital abnormalities.

## Statistical analysis

This study employed a retrospective quantitative analysis approach. Descriptive statistical analyses were performed using Excel to examine ADRs associated with the four TKI-targeted drugs and to characterize the subjects involved. For each medication, the ADR symptom count was divided by the total number of ADR reports to obtain the ADR reporting rate. Symptoms with the highest top 20 reporting rates for each drug were considered common adverse reactions. Comparative descriptive analyses of ADR symptom reporting rates were conducted across the four drugs. Descriptive variables were categorized based on both their frequency of occurrence and the percentage of cases they represented.

This study applied both the reporting odds ratio (ROR) and the empirical Bayesian geometric mean (EBGM) methods in the disproportionality analysis to calculate values such as ROR, PRR, and EBGM. The ROR method assesses the strength of association between a drug and an ADR by calculating the ratio of reported odds ratios. In Vigibase, the strength of association between a quantified drug and a specific ADR is more sensitive to possible associations, facilitating early detection of ADR signals and improving signal detection performance. Meanwhile, the EBGM method incorporates prior research findings and known characteristics of drugs into the analysis, yielding more accurate and reliable assessment results. This is especially important when dealing with limited data or rare ADRs, as it allows for better utilization of prior information to make informed inferences. Compared to simpler frequency-counting methods, EBGM offers greater stability, particularly in situations where data fluctuates or noise might distort results. This method helps to more robustly detect real ADR signals, thereby reducing the occurrence of false positives and false negatives. The larger the numerical value, the stronger the statistical correlation between the drug and the ADR, indicating a higher signal intensity.

## Results

### ADR basic information

The first ADR reports for Sorafenib were recorded in 2004, Regorafenib in 2009, Lenvatinib in 2013, and Cabozantinib in 2012. As of 2024, the WHO VigiAccess database contained 112,975 ADR reports related to TKI-targeted drugs, involving Sorafenib (34,711), Regorafenib (17,370), Lenvatinib (27,697), and Cabozantinib (33,197). The analysis presented in Table 2 reveals that excluding 4,644 reports with undisclosed gender, male patients account for 68,209 ADR cases (60.38%), while female patients represent 40,122 cases (35.51%; Fig. 1). This yields a male-to-female ratio of 1.70:1, which is statistically significant. Notably, females typically account for only about a quarter of all HCC cases globally. In the ADR reports related to Lenvatinib, female patients (53.33%) account for a higher proportion than male patients (44.28%, $\chi^2 = 220.6$, $p < 0.001$). This discrepancy may be attributed to the widespread use of Lenvatinib in female-dominant high-prevalence cancers, such as thyroid cancer, potentially leading to a higher number of ADR reports in women. Additionally, women have lower body weights, yet Lenvatinib is administered at a fixed dose, which may result in higher drug exposure in female patients. Excluding reports where age was not specified, the age group most frequently reporting ADRs was 45 to 64 years. Geographically, the majority of ADR reports originated from the Americas (47.70%), Asia (32.13%), and Europe (19.07%). This suggests that the choice of TKI drugs may vary across regions. Figure 2 summarizes the annual distribution of ADR reports for each drug.

### Distribution of 20 SOCs

Further analysis was conducted on the reporting rates of 20 SOCs for the four TKI-targeted drugs (Table 3). The four drugs exhibited relatively high incidences of adverse events in gastrointestinal disorders, general disorders and administration site conditions, and investigations. Cabozantinib had the highest incidence of gastrointestinal disorders (22.63%). In comparison, the incidence of skin and subcutaneous tissue disorders was significantly lower for Lenvatinib (5.00%) than for Sorafenib (12.60%), Regorafenib (17.69%), and Cabozantinib (10.92%). Lenvatinib was commonly associated with nervous system disorders and vascular disorders.

The top five most frequently reported adverse event types of TKI-targeted drugs included gastrointestinal disorders (76,251, 19.59%), general disorders and administration site conditions (57,567, 14.79%), skin and subcutaneous tissue disorders (46,474, 11.94%), investigations (30,875, 7.93%), and nervous system disorders (23,277, 5.98%).

### Most common ADRs

Table 4 details the 20 most frequently reported ADRs of the four drugs. The common ADRs across all four drugs included diarrhea, fatigue, rash, nausea, decreased appetite, asthenia, off-label use, vomiting, and headache. Sorafenib and Regorafenib were more frequently associated with palmar-plantar erythrodysesthesia syndrome, while the most common ADRs for Lenvatinib and Cabozantinib were diarrhea and fatigue. Sorafenib exhibited a relatively high reporting rate of ADRs such as rash and asthenia. These common mild ADRs warrant early

| | Sorafenib | Regorafenib | Lenvatinib | Cabozantinib |
|---|---|---|---|---|
| Number of ADR reports | 34,711 | 17,370 | 27,697 | 33,197 |
| Female | 9,192 (26.48%) | 6,688 (38.50%) | 14,772 (53.33%) | 9,470 (28.53%) |
| Male | 23,430 (67.50%) | 9,783 (56.32%) | 12,263 (44.28%) | 22,733 (68.48%) |
| Unknown | 2,089 (6.02%) | 899 (5.18%) | 662 (2.39%) | 994 (2.99%) |
| < 18 years | 331 (0.95%) | 53 (0.31%) | 58 (0.21%) | 150 (0.45%) |
| 18–44 years | 2,057 (5.93%) | 1,001 (5.76%) | 775 (2.80%) | 1,049 (3.16%) |
| 45–64 years | 12,485 (35.97%) | 6,266 (36.07%) | 7,189 (25.96%) | 7,164 (21.58%) |
| 65–74 years | 8,428 (24.28%) | 4,275 (24.61%) | 6,854 (24.75%) | 5,970 (17.98%) |
| ≥ 75 years | 4,634 (13.35%) | 1,887 (10.86%) | 3,980 (14.37%) | 3,211 (9.67%) |
| Unknown | 6,776 (19.52%) | 3,888 (22.38%) | 8,841 (31.92%) | 15,653 (47.15%) |
| Africa | 113 (0.33%) | 42 (0.24%) | 35 (0.13%) | 4 (0.01%) |
| Americas | 12,223 (35.21%) | 7,073 (40.72%) | 11,175 (40.35%) | 23,411 (70.52%) |
| Asia | 13,977 (40.27%) | 5,363 (30.88%) | 13,085 (47.24%) | 3,872 (11.66%) |
| Europe | 8,193 (23.60%) | 4,546 (26.17%) | 3,118 (11.26%) | 5,685 (17.13%) |
| Oceania | 205 (0.59%) | 346 (1.99%) | 284 (1.03%) | 225 (0.68%) |
| 2024 | 1,167 (3.36%) | 1,239 (7.13%) | 7,117 (25.70%) | 5,908 (17.80%) |
| 2023 | 2,018 (5.81%) | 1,290 (7.43%) | 6,327 (22.84%) | 5,059 (15.24%) |
| 2022 | 1,498 (4.32%) | 1,113 (6.41%) | 4,468 (16.13%) | 4,773 (14.38%) |
| 2021 | 1,396 (4.02%) | 1,167 (6.72%) | 2,572 (9.29%) | 3,695 (11.13%) |
| 2020 | 1,739 (5.01%) | 1,584 (9.12%) | 2,168 (7.83%) | 2,990 (9.01%) |
| 2019 | 2,052 (5.91%) | 1,802 (10.37%) | 2,489 (8.99%) | 6,103 (18.38%) |
| 2018 | 2,374 (6.84%) | 2,015 (11.60%) | 1,228 (4.43%) | 2,374 (7.15%) |
| 2017 | 4,035 (11.62%) | 1,532 (8.82%) | 819 (2.96%) | 1,267 (3.82%) |
| 2016 | 2,722 (7.84%) | 2,086 (12.01%) | 423 (1.53%) | 168 (0.51%) |
| 2015 | 3,332 (9.60%) | 1,676 (9.65%) | 83 (0.30%) | 445 (1.34%) |
| 2014 | 3,095 (8.92%) | 1,624 (9.35%) | 2 (0.01%) | 414 (1.25%) |
| Before 2013 | 9,283 (26.74%) | 242 (1.39%) | 1 (0.00%) | 1 (0.00%) |

**Table 2**. Characteristics of ADR reports of four common targeted drugs.

intervention to alleviate patient discomfort, which can be achieved through timely adjustment of the drug regimen, appropriate symptomatic treatment, or detailed medication instructions, thereby effectively improving patient compliance.

Most of the top 20 most frequently reported AEs were self-limiting and mild. However, a few notable events, including pain in extremities, death, and malignant neoplasm progression, were also reported.

## Serious adverse events

Serious adverse events were also identified through the WHO-VigiAccess database, including life-threatening events, deaths, and severe ADRs requiring hospitalization. The proportions of serious ADRs observed with Sorafenib, Regorafenib, Lenvatinib, and Cabozantinib were 1.97%, 1.94%, 0.93%, and 1.72%, respectively (Fig. 3).

## ADR reporting and signaling detection

The ROR method was employed to assess the statistical correlation between each targeted drug and its associated ADRs. Positive signals were detected and ranked based on signal intensity (the lower limit of the 95% confidence interval of the ROR value) and the number of reports, as shown in Table 5 and Sup-Table 1.

In the Regorafenib group, the most prominent signal was for metastatic colorectal cancer, with an ROR of 447.75. The Lenvatinib group presented the strongest signal for immune-mediated hypothyroidism, with an ROR of 77.96. As for the Cabozantinib group, the strongest signal was for hair color changes, with an ROR of 26.48.

Diarrhea and fatigue were the most frequently reported adverse reactions across all four drugs. Notably, palmar-plantar erythrodysaesthesia syndrome was more frequently reported in the Sorafenib and Regorafenib groups, with 3,746 and 2,496 cases, respectively.

## Common and distinctive ADRs

A comparison of the top 20 ADRs reported for each TKI-targeted drug revealed 145 identical signals in the PT terms of the four drugs (Table 6). The SOC with the highest number of adverse signals was general disorders and administration site conditions. The top five most frequently reported ADRs within this category included asthenia, drug ineffectiveness, gait disturbance, inability to walk, and peripheral edema. Additionally, there were over 10 shared signals among gastrointestinal disorders (18), investigations (13), skin and subcutaneous tissue disorders (14), respiratory, thoracic and mediastinal disorders (11), and nervous system disorders (15).

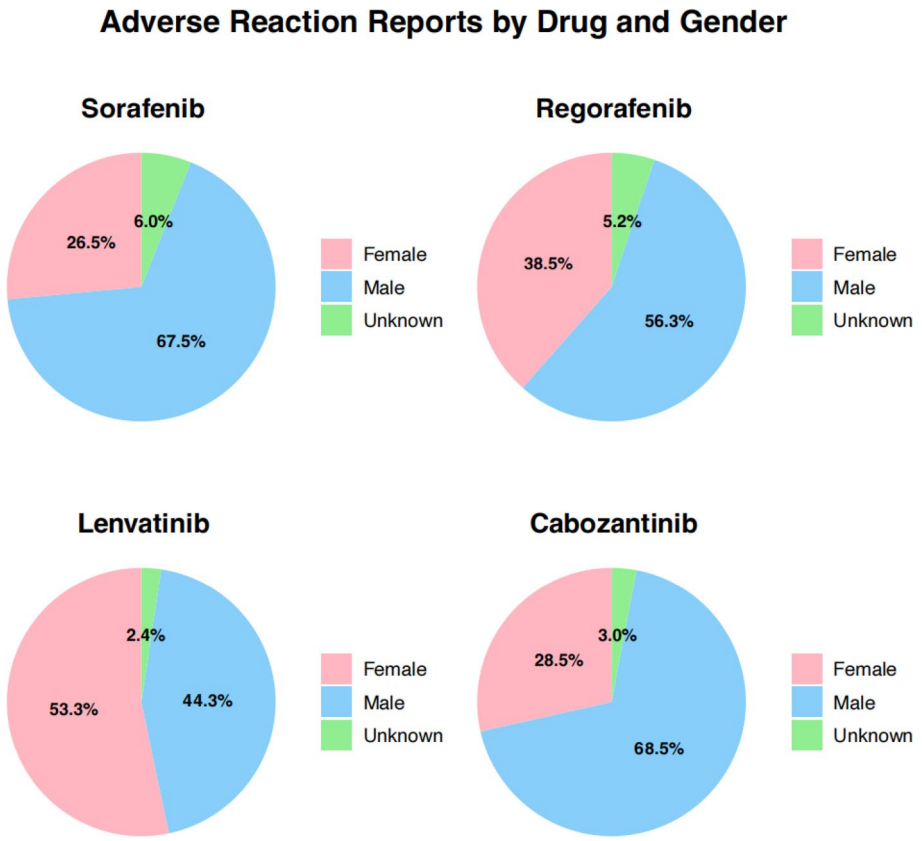


**Fig. 1**. The gender percentage of common ADR reports for four drugs.

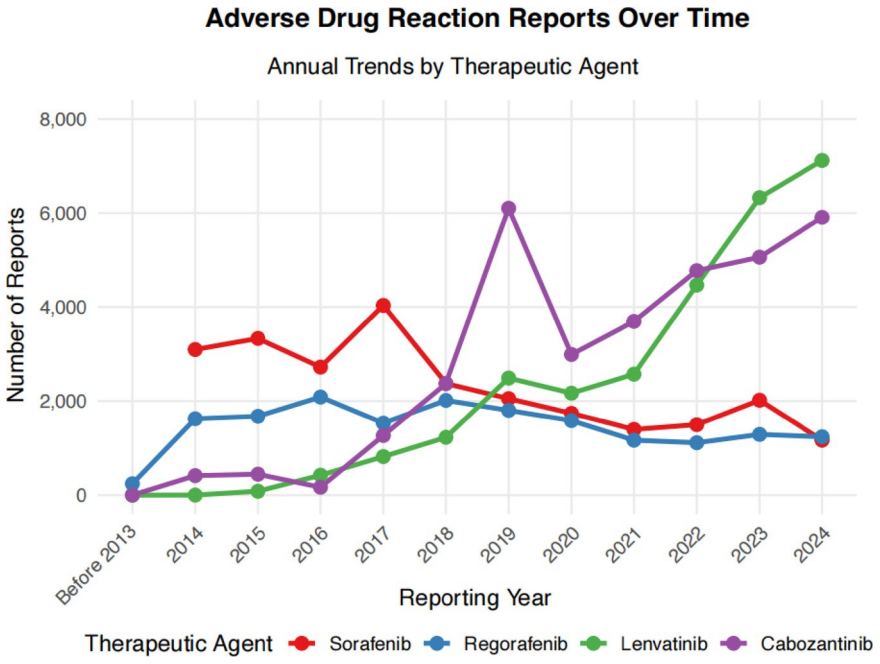


**Fig. 2**. The number of ADRs reported per year.

| | Sorafenib (*N* = 112,612) | Regorafenib (*N* = 67,890) | Lenvatinib (*N* = 80,856) | Cabozantinib (*N* = 127,861) |
|---|---|---|---|---|
| Blood and lymphatic system disorders | 917 (1.35%) | 2456 (2.18%) | 1235 (1.53%) | 1043 (0.82%) |
| Cardiac disorders | 570 (0.84%) | 1629 (1.45%) | 1499 (1.85%) | 1014 (0.79%) |
| Eye disorders | 320 (0.47%) | 568 (0.50%) | 416 (0.51%) | 710 (0.56%) |
| Gastrointestinal disorders | 10,505 (15.47%) | 21,350 (18.96%) | 15,463 (19.12%) | 28,933 (22.63%) |
| General disorders and administration site conditions | 11,699 (17.23%) | 15,634 (13.88%) | 10,623 (13.14%) | 19,611 (15.34%) |
| Hepatobiliary disorders | 1610 (2.37%) | 2324 (2.06%) | 1595 (1.97%) | 1240 (0.97%) |
| Infections and infestations | 1774 (2.61%) | 3195 (2.84%) | 2785 (3.44%) | 3898 (3.05%) |
| Injury, poisoning and procedural complications | 3641 (5.36%) | 4451 (3.95%) | 2428 (3.00%) | 7640 (5.98%) |
| Investigations | 4993 (7.36%) | 7248 (6.44%) | 8034 (9.94%) | 10,600 (8.29%) |
| Metabolism and nutrition disorders | 2877 (4.24%) | 4655 (4.13%) | 4807 (5.95%) | 6014 (4.70%) |
| Musculoskeletal and connective tissue disorders | 3456 (5.09%) | 4927 (4.38%) | 3586 (4.44%) | 5440 (4.26%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 3827 (5.64%) | 5137 (4.56%) | 2961 (3.66%) | 4666 (3.65%) |
| Nervous system disorders | 3858 (5.68%) | 5646 (5.01%) | 5577 (6.90%) | 8196 (6.41%) |
| Psychiatric disorders | 1095 (1.61%) | 1934 (1.72%) | 1344 (1.66%) | 1746 (1.37%) |
| Renal and urinary disorders | 991 (1.46%) | 1386 (1.23%) | 2199 (2.72%) | 1543 (1.21%) |
| Reproductive system and breast disorders | 233 (0.34%) | 477 (0.42%) | 277 (0.34%) | 387 (0.30%) |
| Respiratory, thoracic and mediastinal disorders | 3672 (5.41%) | 4940 (4.39%) | 4513 (5.58%) | 6064 (4.74%) |
| Skin and subcutaneous tissue disorders | 8555 (12.60%) | 19,915 (17.69%) | 4040 (5.00%) | 13,964 (10.92%) |
| Surgical and medical procedures | 711 (1.05%) | 927 (0.82%) | 425 (0.53%) | 323 (0.25%) |
| Vascular disorders | 1887 (2.78%) | 2723 (2.42%) | 3991 (4.94%) | 2763 (2.16%) |

**Table 3**. ADR number and report rate of 20 SOCs of four common targeted drugs. %: The number of ADR reports for each SOC as a percentage of the total number of reports.

| Sorafenib (*N* = 34,711) | | Regorafenib (*N* = 17,370) | | Lenvatinib (*N* = 27,697) | | Cabozantinib (*N* = 33,197) | |
|---|---|---|---|---|---|---|---|
| ADR | Report rate % | ADR | Report rate % | ADR | Report rate % | ADR | Report rate % |
| Diarrhea | 4.86 | Fatigue | 4.19 | Diarrhea | 4.09 | Diarrhea | 6.12 |
| Palmar-plantar erythrodysaesthesia syndrome | 3.33 | Palmar-plantar erythrodysaesthesia syndrome | 3.68 | Fatigue | 3.53 | Fatigue | 4.68 |
| Rash | 2.61 | Off label use | 3.28 | Hypertension | 3.23 | Nausea | 3.12 |
| Fatigue | 2.42 | Diarrhea | 3.10 | Decreased appetite | 2.82 | Decreased appetite | 2.84 |
| Decreased appetite | 2.22 | Decreased appetite | 2.54 | Malignant neoplasm progression | 2.53 | Off label use | 2.81 |
| Nausea | 1.97 | Asthenia | 2.03 | Nausea | 2.45 | Palmar-plantar erythrodysaesthesia syndrome | 1.91 |
| Off label use | 1.92 | Dysphonia | 1.93 | Blood pressure increased | 2.18 | Weight decreased | 1.89 |
| Asthenia | 1.74 | Hypertension | 1.82 | Vomiting | 1.95 | Stomatitis | 1.83 |
| Death | 1.66 | Pain in extremity | 1.61 | Asthenia | 1.91 | Malignant neoplasm progression | 1.76 |
| Hepatocellular carcinoma | 1.60 | Nausea | 1.56 | Weight decreased | 1.59 | Blood pressure increased | 1.74 |
| Pain in extremity | 1.45 | Death | 1.52 | Hypothyroidism | 1.58 | Death | 1.67 |
| Abdominal pain | 1.42 | Weight decreased | 1.51 | Dehydration | 1.37 | Asthenia | 1.61 |
| Alopecia | 1.33 | Pyrexia | 1.50 | Headache | 1.34 | Vomiting | 1.42 |
| Vomiting | 1.32 | Rash | 1.40 | Rash | 1.05 | Constipation | 1.40 |
| Pruritus | 1.26 | Abdominal pain | 1.16 | Stomatitis | 0.98 | Blister | 1.28 |
| Weight decreased | 1.25 | Pain | 1.08 | Arthralgia | 0.95 | Pain in extremity | 1.08 |
| Hypertension | 1.22 | Vomiting | 1.08 | Constipation | 0.88 | Hypertension | 1.06 |
| Blister | 1.12 | Constipation | 1.05 | Abdominal pain | 0.86 | Rash | 1.06 |
| Pyrexia | 1.01 | Headache | 1.01 | Dysphonia | 0.85 | Taste disorder | 0.97 |
| Skin exfoliation | 0.89 | Colorectal cancer metastatic | 0.98 | Palmar-plantar erythrodysaesthesia syndrome | 0.85 | Dysphonia | 0.92 |

**Table 4**. Top 20 ADRs of four common targeted drugs. %: Percentage of total number of reports for each common ADR.

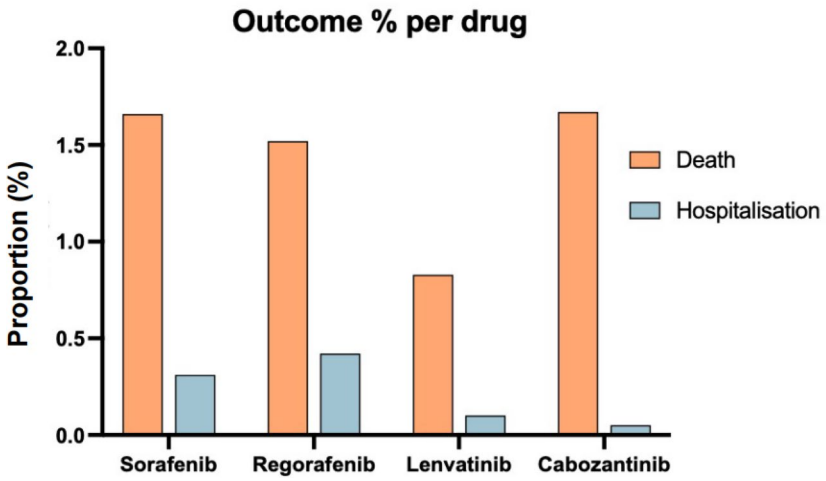


**Fig. 3**. Serious adverse reactions to four TKI targeted drugs.

When comparing the top 20 ADRs reported for each TKI drug within their respective SOCs, distinct ADRs were identified (Table 7). All four drugs exhibited specific ADRs in gastrointestinal disorders, general disorders and administration site conditions, investigations, and hepatobiliary disorders. Sorafenib was frequently associated with aphthous ulcers, gastritis, acute pancreatitis, esophageal varices hemorrhage, and gingival bleeding. Regorafenib was commonly linked with changes in bowel habits, gastrointestinal motility disorders, proctalgia, and lower abdominal pain. Lenvatinib manifested in immune-mediated enterocolitis, large intestine perforation, and intestinal perforation. Cabozantinib was associated with toothache, glossitis, oral mucosal blistering, gingival pain, tongue discomfort, tooth disorder, tongue ulceration, and hemorrhoids. The groups treated with Sorafenib, Regorafenib, Lenvatinib, and Cabozantinib exhibited 13, 12, 17, and 12 distinct symptoms, respectively.

## Discussion

A significant challenge in the field of oncology is the effective treatment of HCC, which continues to represent a major threat to human health[1]. While immune-based therapies (e.g., Atezolizumab/Bevacizumab) have become the first-line standard of care for advanced HCC, TKIs remain crucial for second-line treatment options. Consequently, the core value of this study lies in providing actionable clinical recommendations for the individualized monitoring of patients undergoing second-line therapy. The SRS is a pivotal tool in pharmacovigilance, designed to collect and monitor adverse reactions following the market release of pharmaceutical products. The SRS identifies and evaluates potential drug-related risks, encompassing both known and emerging ADRs, providing essential data for continuous drug safety surveillance[18]. Currently, most drug safety signal studies rely on data from three major global databases: the EudraVigilance Data Analysis System (EVDAS), the US FDA Adverse Event Reporting System (FAERS), and the WHO VigiBase. The VigiBase database, publicly accessible and underpinned by the SRS framework, aids regulatory authorities, researchers, and healthcare professionals worldwide in advancing the understanding of drug safety and making evidence-based decisions[19].

As of 2024, the WHO had received a total of 112,975 ADR reports associated with TKI-targeted drugs, including Sorafenib (34,711), Regorafenib (17,370), Lenvatinib (27,697), and Cabozantinib (33,197). Among these reports, 68,209 ADR cases (60.38%) were from male patients, surpassing the 40,122 cases (35.51%) from female patients, resulting in a male-to-female ratio of 1.70:1. This number represents a statistically significant difference. This might be attributed to the higher incidence of HCC in men compared to women. According to GLOBOCAN 2022 data, the global average incidence rate ratio (IRR) of HCC in men and women is 2.2, with an age-standardized IRR of 2.6[20]. Across all continents, HCC is more prevalent in men, with IRR levels ranging from 1.2 to 2.5. The underlying reasons for this gender difference remain obscure, though it may be partly related to the more pronounced impact of HBV infection on HCC development in men compared to women. Notably, in the ADR reports related to Lenvatinib, the proportion of female patients (53.33%) is higher than that of male patients (44.28%). The widespread use of Lenvatinib in female-dominant high-prevalence cancers, such as thyroid cancer, may have indirectly contributed to the higher proportion of ADR reports among women.

Excluding reports with unspecified age, the age group most frequently reporting ADRs is 45 to 64 years old. Most ADR reports originate from the Americas, Asia, and Europe, accounting for 47.70%, 32.13%, and 19.07% of the total, respectively. This distribution suggests that there may be regional differences in the selection of TKI drugs. Notably, Europe and Oceania exhibit relatively fewer ADR reports. This might be attributed to factors such as limited social mobilization efforts, inadequate accessibility to ADR reporting systems, and low coverage of information systems[21]. Additionally, women are more likely to report symptoms proactively, as they tend to be more attentive to health details, whereas men may underreport mild ADRs due to cultural attitudes promoting toughness[22]. In regions with scarce healthcare resources, patients may underutilize healthcare services due to mistrust in the healthcare system, and rare ADRs may be misdiagnosed as disease progression because of the

| Sorafenib | | | Regorafenib | | | Lenvatinib | | | Cabozantinib | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PT | Number | 95%CI -(ROR) | PT | Number | 95%CI -(ROR) | PT | Number | 95%CI -(ROR) | PT | Number | 95%CI -(ROR) |
| Thyroid cancer | 131 | 11.98 | Colorectal cancer metastatic | 666 | 447.75 | Immune-mediated hypothyroidism | 247 | 77.96 | Hair colour changes | 467 | 26.48 |
| Papillary thyroid cancer | 31 | 10.40 | Colorectal cancer | 459 | 234.27 | Immune-mediated hyperthyroidism | 41 | 21.52 | Tooth disorder | 254 | 10.44 |
| Keratoacanthoma | 35 | 8.82 | Colon cancer | 255 | 74.91 | Cytokine release syndrome | 35 | 16.06 | Taste disorder | 1,235 | 8.82 |
| Graft versus host disease | 26 | 8.67 | Rectal cancer | 80 | 52.75 | Arterial haemorrhage | 27 | 12.25 | Nasal ulcer | 73 | 6.76 |
| Acute myeloid leukaemia | 56 | 7.56 | Carcinoembryonic antigen increased | 104 | 36.08 | Immune-mediated adrenal insufficiency | 40 | 12.05 | Inappropriate schedule of product administration | 1,030 | 6.19 |
| Hepatic cancer | 293 | 7.20 | Colon cancer metastatic | 56 | 32.37 | Type 1 diabetes mellitus | 55 | 11.53 | Prostatic specific antigen increased | 34 | 6.17 |
| Hepatocellular carcinoma | 1,798 | 6.47 | Gastrointestinal stromal tumour | 108 | 14.71 | Immune-mediated enterocolitis | 93 | 10.53 | Product prescribing issue | 162 | 6.13 |
| Squamous cell carcinoma | 40 | 6.29 | Stoma site haemorrhage | 33 | 13.84 | Immune-mediated myocarditis | 29 | 8.56 | Adverse drug reaction | 984 | 5.71 |
| Dermatitis exfoliative | 37 | 5.79 | Palliative care | 42 | 12.77 | Immune-mediated myositis | 16 | 8.09 | Dysgeusia | 896 | 5.29 |
| Malabsorption | 26 | 5.57 | Change of bowel habit | 71 | 5.84 | Immune-mediated encephalitis | 20 | 7.56 | Ageusia | 535 | 5.23 |
| Palmoplantar keratoderma | 182 | 5.57 | Colon cancer recurrent | 11 | 5.77 | Product use issue | 447 | 7.11 | Cell death | 33 | 4.71 |
| Hepatic cancer stage iv | 16 | 5.21 | Rectal adenocarcinoma | 9 | 5.40 | Carbohydrate antigen 125 increased | 16 | 7.02 | Skin ulcer | 924 | 4.49 |
| Skin reaction | 421 | 4.97 | Exercise tolerance decreased | 58 | 5.30 | Myocarditis | 88 | 7.00 | Back disorder | 38 | 3.87 |
| Hypotrichosis | 15 | 4.87 | Metastases to liver | 256 | 5.12 | Immune-mediated pancreatitis | 21 | 6.87 | Hepatic cytolysis | 101 | 3.74 |
| Therapeutic embolisation | 14 | 4.52 | Pre-existing condition improved | 37 | 4.22 | Tracheal fistula | 21 | 6.87 | Product dose omission issue | 764 | 3.33 |
| Neurotoxicity | 34 | 4.45 | Tumour perforation | 7 | 4.08 | Thyroiditis | 81 | 6.25 | Hypertransaminasaemia | 118 | 3.19 |
| Squamous cell carcinoma of skin | 45 | 4.34 | Disability | 7 | 4.08 | Myasthenia gravis | 30 | 6.04 | Renal cancer metastatic | 40 | 3.18 |
| Gastric antral vascular ectasia | 13 | 4.18 | Thermohyperaesthesia | 9 | 3.84 | Immune-mediated myasthenia gravis | 12 | 5.95 | Wrong technique in product usage process | 129 | 3.14 |
| Gastritis haemorrhagic | 13 | 4.18 | Therapeutic product ineffective | 38 | 3.83 | Fulminant type 1 diabetes mellitus | 16 | 5.93 | Arthropathy | 80 | 3.14 |
| Non-small cell lung cancer | 17 | 4.08 | Hyperthermia | 16 | 3.72 | Adrenal insufficiency | 232 | 5.75 | Genital blister | 18 | 3.11 |

**Table 5**. Top 20 PTs for signal strength sorting of four common targeted drugs. (The ROR 95%CI- >1 suggests that there may be a positive association between the drug and the ADR, i.e. in which the use of the drug is more likely to result in the ADR than the non-use of the drug.).

lack of specialized pharmacists, as seen in Africa. Variations in monitoring systems should also be considered. While Europe benefits from real-time monitoring through the EudraVigilance system, low- and middle-income countries still rely on paper-based reporting, resulting in data delay or missing[23]. The application of machine learning techniques, such as random forest algorithms and deep learning with graph neural networks, can efficiently promote the accuracy and efficiency of ADR predictions[24].

The four TKI-targeted drugs commonly induce adverse reactions such as diarrhea, fatigue, rash, nausea, decreased appetite, shortness of breath, off-label use, vomiting, and headache. Diarrhea and nausea may result from the stimulation of the gastrointestinal mucosa, leading to mucosal damage and the subsequent release of 5-hydroxytryptamine (5-HT) by chromaffin cells on the mucosa[25,26]. This triggers nerve impulses that are transmitted to the vomiting center, causing vomiting. These symptoms can be alleviated with medications such as phenothiazines, butyrophenones, metoclopramide, and 5-HT3 antagonists. Sorafenib and Regorafenib are particularly prone to causing palmar-plantar erythrodysesthesia syndrome and rash. In addition to these common mild ADRs, serious adverse events warrant special attention. For instance, death is reported as a common ADR for Regorafenib, with a reporting rate of up to 1.52%. In the Lenvatinib group, malignant neoplasm progression is reported at a rate of 2.53%. Another noteworthy ADR is off-label use, underscoring the need for enhanced biomedical training for healthcare professionals to ensure a thorough understanding of drug indications and contraindications[27]. It is also crucial to conduct further clinical studies to evaluate the safety and efficacy of drugs used off-label, including those for different indications, doses, routes, or populations. Additionally, improving the transparency of drug information, such as drug package inserts, clinical study results,

| System organ classes | ADRs | Signal *N* |
|---|---|---|
| Blood and lymphatic system disorders | Anaemia, Neutropenia, Thrombocytopenia | 3 |
| Cardiac disorders | Myocardial infarction, Cardiac failure, Atrial fibrillation | 3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Malignant neoplasm progression | 1 |
| Endocrine disorders | Hypothyroidism | 1 |
| Eye disorders | Vision blurred, Visual impairment | 2 |
| Gastrointestinal disorders | Dysphagia, Glossodynia, Nausea, Abdominal distension, Oral pain, Constipation, Flatulence, Mouth ulceration, Dyspepsia, Gastrointestinal disorder, Abdominal pain, Vomiting, Ascites, Diarrhoea, Stomatitis, Abdominal pain upper, Abdominal discomfort, Dry mouth | 18 |
| General disorders and administration site conditions | Asthenia, Drug ineffective, Gait disturbance, Gait inability, Oedema peripheral, Swelling, Condition aggravated, Oedema, Chest pain, General physical health deterioration, Fatigue, Death, Mucosal inflammation, Chills, Pyrexia, Feeling abnormal, Drug intolerance, Adverse event, Peripheral swelling, Pain, Disease progression, Malaise | 22 |
| Hepatobiliary disorders | Hepatic function abnormal, Liver disorder | 2 |
| Infections and infestations | Urinary tract infection, Nasopharyngitis, Pneumonia, Sepsis, Infection | 5 |
| Injury, poisoning and procedural complications | Off label use, Fall, Toxicity to various agents, Product dose omission issue, Contusion | 5 |
| Investigations | Blood glucose increased, Alanine aminotransferase increased, Heart rate increased, Weight decreased, Weight increased, Blood creatinine increased, Blood bilirubin increased, Platelet count decreased, Hepatic enzyme increased, Blood pressure increased, White blood cell count decreased, Haemoglobin decreased, Aspartate aminotransferase increased | 13 |
| Metabolism and nutrition disorders | Hyponatraemia, Dehydration, Hypokalaemia, Feeding disorder, Decreased appetite, Hypophagia | 6 |
| Musculoskeletal and connective tissue disorders | Joint swelling, Muscle spasms, Back pain, Pain in extremity, Myalgia, Arthralgia, Bone pain, Muscular weakness, Neck pain | 9 |
| Nervous system disorders | Tremor, Memory impairment, Hypoaesthesia, Dysgeusia, Dizziness, Headache, Paraesthesia, Burning sensation, Neuropathy peripheral, Somnolence, Seizure, Balance disorder, Lethargy, Cerebrovascular accident, Loss of consciousness | 15 |
| Psychiatric disorders | Confusional state, Eating disorder, Anxiety, Insomnia, Depression | 5 |
| Renal and urinary disorders | Renal failure, Proteinuria, Renal impairment, Haematuria, Acute kidney injury | 5 |
| Respiratory, thoracic and mediastinal disorders | Haemoptysis, Cough, Oropharyngeal pain, Productive cough, Epistaxis, Pulmonary embolism, Aphonia, Pleural effusion, Dysphonia, Interstitial lung disease, Dyspnoea | 11 |
| Skin and subcutaneous tissue disorders | Skin discolouration, Blister, Skin exfoliation, Rash, Palmar-plantar erythrodysaesthesia syndrome, Dry skin, Hyperkeratosis, Skin ulcer, Skin disorder, Alopecia, Rash pruritic, Acne, Erythema, Pruritus | 14 |
| Surgical and medical procedures | Hospitalisation | 1 |
| Vascular disorders | Blood pressure fluctuation, Haemorrhage, Hypotension, Hypertension | 4 |

**Table 6**. Same ADRs among four common targeted drugs.

and pharmacovigilance data, will enable healthcare providers and patients to make more informed decisions. Furthermore, patients should be actively involved in the decision-making process regarding off-label use, with adequate information and education provided to help them understand the associated risks and benefits.

Common adverse reactions induced by TKI-targeted drugs, such as diarrhea, malaise, rash, palmoplantar erythema syndrome, and loss of appetite, have been widely reported and align with the information provided in the drug inserts. Therefore, monitoring for potential risks during clinical use is crucial. Moreover, patients should be advised to implement prophylactic measures, such as using urea creams at an early stage, and undergo regular monitoring. In the Lenvatinib treatment group, blood pressure abnormalities were reported more frequently, highlighting the need for close monitoring of blood pressure in patients with comorbid hypertension during treatment with Lenvatinib[28]. Among the top 20 PTs with strong signal intensities in the Sorafenib and Regorafenib treatment groups, the most notable signals were associated with malignant tumors, such as thyroid cancer and metastatic colorectal cancer. In contrast, the Lenvatinib group was often accompanied by adverse immune system reactions, such as cytokine release syndrome[29]. Cabozantinib, on the other hand, shows relatively milder adverse effects, including hair color changes, tooth disorders, and taste disorders. When TKI-targeted drugs are used for adjuvant treatment in cancer patients, ADRs such as tumor metastasis and progression may be observed. For serious ADR signals, close monitoring should be done with patients supervised for checkups. However, given the inherent nature of malignant tumors, which often exhibit local infiltration and distant metastasis, it is difficult to attribute tumor progression solely to drug-induced ADRs.

## Limitation

This study primarily utilized the SRS database while acknowledging its inherent limitations. SRS is susceptible to various biases, such as visibility bias, selection bias, and underreporting, all of which may influence the study's findings. For instance, the utilization of diverse TKI-targeted drugs can vary across regions, and underreporting in certain areas may skew the results. Additionally, the inherent biases within the SRS, such as the underreporting of mild ADRs and visibility bias (e.g., Sorafenib is more frequently reported due to its longer historical use), may affect the accuracy of the signals detected. Furthermore, the regional representation of the data is limited, with a disproportionately high amount of data coming from high-income countries, which may lead to an underestimation of ADR characteristics in low- and middle-income regions.

| | Sorafenib | Regorafenib | Lenvatinib | Cabozantinib |
|---|---|---|---|---|
| Blood and lymphatic system disorders | Leukopenia, Pancytopenia, Lymphadenopathy | Disseminated intravascular coagulation | | |
| Cardiac disorders | Acute myocardial infarction | | Myocarditis, Cardiomyopathy | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | Thyroid cancer, Neoplasm malignant | Metastases to peritoneum, Metastases to lymph nodes, Colon cancer metastatic, Colorectal cancer, Gastrointestinal stromal tumour, Rectal cancer, Colorectal cancer metastatic, Colon cancer | Tumour haemorrhage | Neoplasm |
| Congenital, familial and genetic disorders | | | | |
| Ear and labyrinth disorders | | Vertigo | | |
| Endocrine disorders | | | Immune-mediated hypothyroidism, Immune-mediated hyperthyroidism, Thyroiditis | |
| Eye disorders | | | | |
| Gastrointestinal disorders | Aphthous ulcer, Gastritis, Pancreatitis acute, Oesophageal varices haemorrhage, Gingival bleeding | Change of bowel habit, Gastrointestinal motility disorder, Proctalgia, Abdominal pain lower | Immune-mediated enterocolitis, Large intestine perforation, Intestinal perforation | Toothache, Glossitis, Oral mucosal blistering, Gingival pain, Tongue discomfort, Tooth disorder, Tongue ulceration, Haemorrhoids |
| General disorders and administration site conditions | Discomfort, Unevaluable event, Swelling face, Feeling hot, Influenza like illness | Multiple organ dysfunction syndrome, Exercise tolerance decreased | Ill-defined disorder, Drug interaction | Tenderness, Ulcer |
| Hepatobiliary disorders | Hepatic cirrhosis | Ocular icterus, Drug-induced liver injury | Cholecystitis, Cholangitis, Immune-mediated hepatic disorder, Cholecystitis acute | Hypertransaminasaemia, Hepatic cytolysis |
| Immune system disorders | | | | |
| Infections and infestations | Gastroenteritis | | Septic shock, Cystitis | Candida infection |
| Injury, poisoning and procedural complications | | | Incorrect dose administered | Wrong technique in product usage process, Wound, Overdose, Product prescribing issue |
| Investigations | Alpha 1 foetoprotein increased, Lipase increased | Carcinoembryonic antigen increased, International normalised ratio increased, Blood test abnormal, Full blood count abnormal, Tumour marker increased, Body temperature increased | Protein urine present, Heart rate decreased, Neutrophil count decreased, Thyroid function test abnormal, Electrocardiogram qt prolonged | Thyroid hormones increased, Red blood cell count decreased, Blood potassium increased |
| Metabolism and nutrition disorders | Fluid intake reduced, Hyperglycaemia, Hypophosphataemia, Hypoglycaemia | | Type 1 diabetes mellitus, Electrolyte imbalance, Diabetes mellitus, Tumour lysis syndrome | Appetite disorder, Hypomagnesaemia |
| Musculoskeletal and connective tissue disorders | Flank pain | | Fistula | Pain in jaw, Arthropathy |
| Nervous system disorders | | Dysstasia | Posterior reversible encephalopathy syndrome, Aphasia, Altered state of consciousness, Migraine, Transient ischaemic attack | |
| Pregnancy, puerperium and perinatal conditions | | | | |
| Product issues | | | | |
| Psychiatric disorders | | Poor quality sleep | Delirium, Hallucination | |
| Renal and urinary disorders | | Urinary retention | Nephrotic syndrome | |
| Reproductive system and breast disorders | | | Vaginal haemorrhage | Genital rash |
| Respiratory, thoracic and mediastinal disorders | Hiccups | | Pneumonitis | Dry throat, Nasal dryness, Throat irritation, Nasal ulcer |
| Skin and subcutaneous tissue disorders | Rash papular, Dermatitis, Dermatitis bullous | Stevens-johnson syndrome, Night sweats | | Hair colour changes, Sensitive skin |
| Social circumstances | | Bedridden | | |
| Surgical and medical procedures | | Therapy cessation, Palliative care, Surgery | | |
| Vascular disorders | Flushing | | Internal haemorrhage | |

**Table 7**. Different ADRs among four common targeted drugs.

Furthermore, due to data privacy regulations protecting patient confidentiality, we were unable to access granular patient-level diagnostic details (e.g., primary tumor site, molecular subtyping, or prior treatment history). Additionally, the cross-indication applications of certain TKIs—such as Lenvatinib, which is approved for both renal cell carcinoma and differentiated thyroid cancer—introduce unavoidable heterogeneity, meaning our cohort may include a subset of non-HCC patients. This limitation is inherent to pharmacovigilance databases

like VigiAccess, which requires physicians to make specific considerations for the clinical application of TKIs in their patients.

## Conclusion

This study provides a comprehensive overview of the ADR profiles associated with four TKIs used in HCC treatment, underscoring the importance of individualized monitoring in second-line therapy. While immunotherapy has reshaped the treatment landscape for advanced HCC, TKIs continue to play a vital role in backline therapy. By optimizing strategies for managing ADRs, integrating emerging technologies, and focusing on vulnerable populations, the safety of targeted therapies and the overall quality of patient survival can be significantly enhanced.

## Data availability

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

Received: 22 November 2024; Accepted: 24 April 2025
Published online: 09 May 2025

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## Author contributions

ZW performed statistical analysis of the data from WHO-VigiAccess and wrote the manuscript. ZW and SJ

collected the database from WHO-VigiAccess. XZ contributed to the review and editing of the manuscript. All authors contributed to the article and approved the submitted version.

## Funding
Not applicable.

## Declarations

## Conflict of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Additional information
**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-00004-7.

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