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Haemorrhage-related adverse events profles of lenvatinib and pembrolizumab alone or in combination: a real-world pharmacovigilance study based on FAERS database

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Abstract

Objective Limited understanding exists regarding the haemorrhagic risk resulting from potential interactions between lenvatinib and pembrolizumab. We investigated haemorrhagic adverse events (ADEs) associated with co-administration of lenvatinib and pembrolizumab using data from the Food and Drug Administration Adverse Event Reporting System (FAERS) in an effort to provide recommendations for their safe and sensible use.

Methods The FAERS database's bleeding events linked to lenvatinib and pembrolizumab were carefully examined. Haemorrhagic signals mining was performed by the reported odds ratios (RORs) and information component (IC), corroborated by additive and multiplicative models.

Results A total of 38,416,055 adverse event cases were analyzed, with 1188 bleeding events records in the lenvatinib alone, 952 bleeding events records in the pembrolizumab alone and 420 bleeding events reports in the combination therapy, respectively. We observed a significantly higher risk of haemorrhage with the combination of lenvatinib and pembrolizumab compare with pembrolizumab alone. In addition, in the baseline model analysis of suspected bleeding adverse reactions, the additive model detected an increased incidence of small intestinal haemorrhage caused by combination therapy, and found no risk signals of tumour haemorrhage and tracheal haemorrhage; the results of multiplicative model are all negative.

Conclusion The analysis of FAERS data reveals different levels of haemorrhagic risk when lenvatinib and pembrolizumab are administered concurrently, highlighting the significance of being cautious when using them in clinical practice.

Keywords Haemorrhage-related adverse events, Lenvatinib, Pembrolizumab, pharmacovigilance, FAERS database

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Introduction

Anti-vascular endothelial growth factor (VEGF) regimens possess the capacity to decrease immunosuppressive pathways through the inhibition of VEGF, thereby promoting the normalization of tumor vessels and the remodeling of the tumor microenvironment [1]. Immune checkpoint inhibitors (ICIs) represent significant advancements in the treatment of malignant tumors in recent years, which play a therapeutic role by relieving the suppression of tumor cells on the immune system and enhancing the body's immune response to tumors [2, 3].

An increasing amount of evidence has emerged to show that angiogenesis inhibitors (AGIs) that target the VEGF signaling pathway, namely anti-VEGF monoclonal antibodies (mAbs), anti-VEGF receptor (VEGFR) mAbs, VEGF soluble decoy receptor that sequesters free available VEGF (VEGF-trap), and tyrosine kinase inhibitors (TKIs) with anti-VEGFR activity, when combined with ICIs can have a synergistic effect against certain solid tumors like renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), endometrial cancer, and melanoma [4–7]. Emerging research has demonstrated that VEGF pathway inhibitors not only exert antiangiogenic effects but also enhance the antitumor efficacy of ICIs by suppressing tumor-mediated immunosuppressive cell activity and facilitating T-cell tumor infiltration [8–10]. This mechanistic synergy underscores the therapeutic potential of combining lenvatinib—a multitargeted tyrosine kinase inhibitor—with pembrolizumab, an anti-PD-1 monoclonal antibody, which has demonstrated significant clinical promise in managing diverse malignancies such as hepatocellular carcinoma and advanced thyroid carcinomas [11, 12]. This combined therapy can function synergistically through diverse mechanisms to bolster tumor eradication.

Lenvatinib, acting as a multi-target kinase inhibitor, specifically targets VEGFRs, pivotal in regulating angiogenesis and maintaining vascular integrity. Inhibiting VEGFRs has the potential to induce endothelial dysfunction and increase vascular permeability, consequently heightening the vulnerability to bleeding events [13, 14]. Pembrolizumab, an immune checkpoint inhibitor, enhances T-cell-mediated immune responses. While not directly correlated with bleeding occurrences, the immune stimulation triggered by pembrolizumab could magnify vascular toxicity when combined with lenvatinib, especially in patients with pre-existing vascular fragility or comorbidities [15]. The synergistic risk of bleeding events in lenvatinib-pembrolizumab combination therapy may arise from two mechanisms: endothelial dysfunction (caused by lenvatinib) and immune-mediated vascular injury (potentially aggravated by pembrolizumab) [16]. Nevertheless, there has not yet been a comprehensive report analyzing the hemorrhage safety profiles of this combined therapy in a real-world context.

In order to provide evidence and guidance for the reasonable and safe clinical therapeutic use of the combination of lenvatinib and pembrolizumab, we retrieved and analyzed bleeding events related to the combination using the FAERS database from 2015Q1 to 2024Q1.

Methods

Data source and extraction

We conducted a retrospective pharmacovigilance study on haemorrhage-related ADEs of lenvatinib and pembrolizumab based on the FAERS database, a publicly accessible database of safety reports voluntarily submitted by medical professionals, pharmaceutical manufacturers, consumers, and patients from various regions in order to systematically assess the safety of lenvatinib + pembrolizumab combination therapy in the post-marketing period [17]. Given the anonymized nature of the FAERS database, it is exempt from the requirement for institutional review board approval. FAERS database is consists of seven datasets, which contain demographic and administrative information (DEMO), drug information (DRUG), information on adverse events (REAC), patient outcomes (OUTC), report sources (RPSR), drug therapy start dates and end dates (THER) and indications for drug administration (INDI) [18].

In the present study, the US FDA-approved generic and brand names of lenvatinib and pembrolizumab, which include LENVATINIB (LENVIMA KISPLYX) and PEMBROLIZUMAB (KEYTRUDA) as the primary suspect (PS) was searched to screen for ADEs. In total, 38,416,055 reports were extracted from the FAERS database. There will inevitably be duplicates of earlier public reports because the database is updated periodically. To ensure a unique report, we selected the most recent FDA_DT when the CASEIDs and FDA_DT (reported data) are the same, and choosing the latest PRIMARYID (reported record ID) in those situations according to FDA's deduplication recommendations [19]. All search terms for haemorrhagic event was determined using the preferred term (PT) "haemorrhage or bleeding" (Standardized Medical Dictionary for Regulatory Activities version 26.1 (MedDRA 26.1), PT code 10055798 or 10005103). Next, we examined every PT in the FAERS database that was connected to haemorrhage. Cases and reports of ADEs related to haemorrhage that indicated the medications were "suspect" were kept, but those that indicated the drugs were "concomitant" or "interacting" were eliminated. Cases were excluded if the time between drug initiation and symptom onset was more than two years. Included cases were double-checked to avoid

duplication. For relevant suspected cases, the following data were collected: sex, age, indication, treatment regimen (drug, target drug initiation and end date), event characteristics (time of onset, response outcome and co-reported events), reported serious outcome, type of reporter, country and year of reporting. After the above steps of deduplication as well as screening of lenvatinib and pembrolizumab data, the haemorrhage-related ADEs of patients treated with lenvatinib, pembrolizumab and lenvatinib + pembrolizumab in the FAERS database used for further analysis were finally obtained, and the detailed screening process is shown in Fig. 1. Ultimately, a combination of medication events was created by merging reports and cases of haemorrhage-related ADEs based on three subgroups: lenvatinib without pembrolizumab, lenvatinib plus pembrolizumab, and lenvatinib plus pembrolizumab.

Data mining and analysis

Disproportionality analyses were used in pharmacovigilance studies to identify specific ADEs and a given medication. It compares the proportion of adverse reports in the target drug to the proportion of adverse reports in all other drugs. Two calculation indicators of disproportionality—the information component (IC) based on the Bayesian statistical method and the reporting odds ratio (ROR) based on the frequentist statistical method—were used in our study to examine the relationship between the drug and haemorrhage-related ADEs. The ADEs signals may be identified in our study when they simultaneously satisfied the two algorithm criteria (lower limit of the 95% CI > 1 and > 0 for ROR and IC, respectively), which would increase signal accuracy and remove some false positive PTs. Tables S1 and S2 provide the equations for the two algorithms as well as the matching thresholds.

If available, clinical characteristics (gender, age, reporting country, reporter and outcome, etc.) of reports associated with target drug-related haemorrhage-related ADEs were analyzed. Furthermore, the time to onset of haemorrhage-related ADEs caused by lenvatinib, pembrolizumab and lenvatinib + pembrolizumab were also calculated. The onset time was calculated as the interval between the start time of drug use (START_DT) and the time of ADE occurrence (EVENT_DT). Reports with date errors (START_DT later than EVENT_DT), inaccurate time entries, and missing specific data were excluded.

To investigate the risk of haemorrhage associated with the lenvatinib + pembrolizumab combination therapy compared to lenvatinib and pembrolizumab monotherapies, we employed additive and multiplicative models to evaluate drug-drug interaction signals (DDIs). The adverse event distribution in a specific drug combination approximates a binomial distribution, hence the use of the SAS program "proc genmod" to implement the additive model with an identity-link function and the multiplicative model with a log-link function. Suspicious drug-drug interactions were analyzed separately

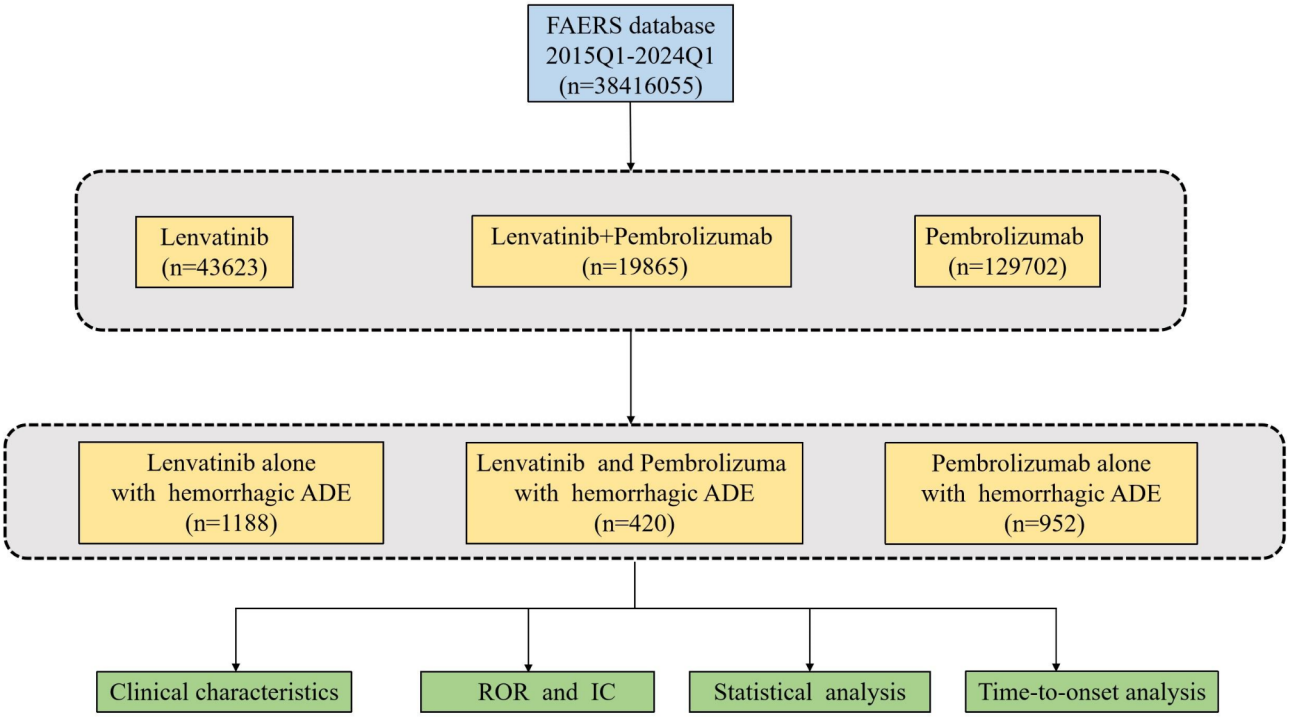

Fig. 1 Flow chart showing the analysis process of the study

[20]. Application of these formulas produced an interaction measure after the initial validation trial, with values greater than 1 (multiplicative model) or 0 (additive model) suggesting evidence of drug interaction [21].

Besides, the additive model captures the cumulative effect between variables, whereas the multiplicative model assesses the interaction effect between variables. By applying both models simultaneously, we may can analyze the relationship between the variables more comprehensively and thus delve into the question of whether the combined treatment of lenvatinib and pembrolizumab increases the risk of bleeding. Their corresponding formulas are as follows:

Additive modeling [20]: The model assumes no interaction if the excess risk of Drug A alone equals the excess risk of Drug A when combined with Drug B:

$$\begin{aligned}&\mathrm{risk(A,notB)}-\mathrm{risk(notA,notB)}=\\&\mathrm{risk(A,B)}-\mathrm{risk(notA,B)},(\mathrm{i.e},\mathrm{RD_{AB}}=\mathrm{RD_A}+\mathrm{RD}_B)\end{aligned}$$

Under the assumption of additive model, in the absence of interactions, the excess risk of the combination is the same as the sum of the excess risks associated with each drug alone. When $RD_{AB} > RD_A + RD_B$ (i.e., $RD_{AB} - RD_A - RD_B > 0$), there is a potential interaction and increased risk for the combination of drugs compared to the expected risk based on the drugs alone.

$$\begin{aligned}\text{Event risk}=&\alpha+\beta\,(\text{drug B})\\&+\delta\,(\text{drugs A and B})+\text{other covariates}\end{aligned}$$

The measure of the interaction is given by the coefficient δ, which is the measure of the difference in the risk of using A and B in combination over the sum of the predictions of using A and B alone. Of particular interest is the statistical deviation of δ from 0, especially the case where δ is greater than 0, which indicates a positive interaction.

Multiplicative modeling [20]: When there is no interaction on the multiplicative scale, the relative risk associated with drug A is the same for no exposure and exposure to drug B. The relative risk associated with drug A is the same for no exposure and exposure to drug B.

$$\begin{aligned}\frac{risk\,(A,notB)}{\mathrm{risk\,(notA,notB)}}=&\frac{\mathrm{risk\,(A,B)}}{\mathrm{risk\,(notA,B)}}\Rightarrow\frac{\mathrm{risk\,(A,B)}}{\mathrm{risk\,(notA,B)}}\\=&\frac{risk\,(A,notB)}{\mathrm{risk\,(notA,notB)}}\times\frac{risk\,(notA,B)}{\mathrm{risk\,(notA,notB)}}\end{aligned}$$

That is, $RR_{AB} = RR_A \times RR_B$, the product of the relative risk associated with a drug combination and the relative risk associated with each drug in the absence of the other is the same, assuming no interaction. Thus, if statistically different from 1, there is evidence of an interaction. In particular, when this ratio is greater than 1, this is an interesting positive interaction from a safety perspective. In this case, the relative risk associated with the combination of the two drugs is greater than the product of the relative risks associated with each drug alone.

Within the framework of log-linear regression (e.g., logistic regression or poisson regression), it is possible to implement formal statistical tests for interaction terms:

$$\begin{aligned}\text{Log (event risk)}=&\alpha+\beta\,(\text{drug A})+\gamma\,(\text{drug B})\\&+\delta\,(\text{drugs A and B})+\text{other covariates}\end{aligned}$$

Whenever the coefficient δ is statistically significantly different from zero, there is evidence of an interaction. When δ is greater than zero, it indicates a positive interaction, implying that the event risk of the combination surpasses the product of the anticipated risks of the two drugs individually. Conversely, when δ is less than zero, it suggests that the relative risk linked with the joint utilization of the two drugs is lower than the product of the relative risks associated with the usage of the two drugs separately. The exponent of δ, exp(δ), serves as the multiplier by which the relative risk of combinatorial use of A and B exceeds the forecasted relative risk of using A and B independently.

All data extraction and statistical analyses were performed by R software (version 4.3.2), SAS software (version 9.4), Microsoft EXCEL 2019 and the Origin software (version 2021).

Result

Descriptive analysis

From January 2015 to March 2024, a total of 38,416,055 ADE reports were extracted from the FAERS database. Following the cleaning of the data, the final analysis included 1,188 bleeding events for lenvatinib alone without pembrolizumab, 952 bleeding events for pembrolizumab alone without lenvatinib, and 420 bleeding events for lenvatinib plus pembrolizumab (Fig. 1).

The clinical baseline features of individuals with haemorrhage-related ADEs for combination therapy, lenvatinib alone, and pembrolizumab alone are listed in Table 1. While the ages of the patients in these three groups were similar, the combination therapy group was observed to have a higher number of female patients. The Americas and Japan were the primary sources of most reports. The percentage of haemorrhage-related ADEs that resulted in death, life-threatening complications, hospitalization, or disability was 87.21% for lenvatinib alone, 47.16% for pembrolizumab alone, and 84.29% for the combined therapy group.

Notably, the percentage of haemorrhage-related ADEs associated with lenvatinib alone increased steadily from 2015 to 2019 (from 2.19 to 17.68%), with a slight decline from 2017 to 2022 (17.68–11.62%); the percentage of haemorrhage-related ADEs associated with

Table 1 Baseline characteristics of haemorrhagic reports associated with lenvatinib, pembrolizumab and combination therapy from 2015 to 2024Q1

Characteristics		Report number, *N* (%)		
		Lenvatinib	Pembrolizumab	Combination therapy
Number of reports		1188	952	420
Gender	Female	435(36.62)	442(46.43)	243(57.86)
	Male	727(61.2)	482(50.63)	174(41.43)
	Unknown or missing	26(2.19)	28(2.94)	3(0.71)
Age (years)	< 18	6(0.51)	10(1.05)	4(0.95)
	18 ≤ and ≤ 64	418(35.19)	295(30.99)	173(41.19)
	> 64	568(47.81)	395(41.49)	190(45.24)
	Unknown or missing	196(16.5)	252(26.47)	53(12.62)
Serious outcome	Death	227(19.11)	132(13.87)	72(17.14)
	Life-threatening	45(3.79)	35(3.68)	13(3.1)
	Hospitalization	751(63.22)	262(27.52)	267(63.57)
	Disability	13(1.09)	20(2.1)	2(0.48)
	Others	152(12.79)	503(52.84)	66(15.71)
Reported Countries (Top five)	Japan	465(39.14)	396(41.6)	82(19.52)
	Americas	400(33.67)	256(26.89)	117(27.86)
	China	107(9.01)	18(1.89)	29(6.9)
	Canada	27(2.27)	18(1.89)	12(2.86)
	France	17(1.43)	36(3.78)	20(4.76)
Reported Person	Physician	647(54.46)	461(48.42)	325(77.38)
	Consumer	413(34.76)	338(35.5)	71(16.9)
	Pharmacist	54(4.55)	51(5.36)	12(2.86)
	Other health-professional	45(3.79)	51(5.36)	11(2.62)
	Unknown	29(2.44)	51(5.36)	1(0.24)
Reporting year	2015	26(2.19)	29(3.05)	/
	2016	60(5.05)	34(3.57)	/
	2017	70(5.89)	50(5.25)	4(0.95)
	2018	149(12.54)	89(9.35)	4(0.95)
	2019	210(17.68)	102(10.71)	27(6.43)
	2020	180(15.15)	89(9.35)	51(12.14)
	2021	154(12.96)	95(9.98)	63(15)
	2022	138(11.62)	148(15.55)	101(24.05)
	2023	175(14.73)	252(26.47)	144(34.29)
	2024Q1	26(2.19)	64(6.72)	26(6.19)

pembrolizumab alone gradually increased from 2015 to 2023 (from 3.05 to 26.47%); and the percentage of haemorrhage-related ADEs for combination therapy significantly increased year over year from 2018 to 2023 (from 0.95 to 34.29%).

The tob 5 most common indications for primary cancer in the FAERS database for lenvatinib、pembrolizumab and combination therapy-induced haemorrhage cases are shown in Table 2. These indications accounted for approximately 79.12%, 29.31%, and 66.19% of all cases meeting inclusion and exclusion criteria, respectively, for lenvatinib, pembrolizumab, and combination therapy. The top 5 indications for which deaths were reported in these haemorrhage cases are shown in Table 2. These indications represented for approximately 15.57%, 4.1%, and 11.43% of all cases meeting inclusion and exclusion criteria, respectively, for lenvatinib, pembrolizumab, and combination therapy.

Signal of disproportionality reporting

Table 3 contains a list of the disproportionality analysis results. Significantly, 20, 10, and 31 PTs emerged as potential signals associated with combination therapy, pembrolizumab monotherapy, and lenvatinib monotherapy, respectively, predominantly concentrated within nervous system and gastrointestinal domains. Table 3 shows that the frequent adverse safety signals for combination therapy were cerebral haemorrhage, upper gastrointestinal haemorrhage, and tumour haemorrhage, the largest ROR values were tumour haemorrhage, tracheal haemorrhage and spinal cord haemorrhage. The frequent adverse reaction signals of lenvatinib were tumour haemorrhage, cerebral haemorrhage and oesophageal varices

Table 2 Top 5 most common indications of primary cancer in the FAERS database for lenvatinib、pembrolizumab and combination therapy-induced bleeding cases and top 5 indications for which deaths were reported in these bleeding cases

drugs	Tob 5 indications	#of patients	%of patients	#of deaths reported	%of deaths reported
lenvatinib	hepatocellular carcinoma	506	42.81%	88	7.45%
	thyroid cancer	221	18.7%	46	3.89%
	hepatic cancer	84	7.11%	11	0.93%
	anaplastic thyroid cancer	75	6.35%	37	3.13%
	renal cancer	49	4.15%	2	0.17%
pembrolizumab	non-small cell lung cancer	97	10.19%	16	1.68%
	uterine cancer	55	5.78%	2	0.21%
	metastatic malignant melanoma	46	4.83%	8	0.84%
	endometrial cancer	41	4.31%	9	0.95%
	transitional cell carcinoma	40	4.2%	4	0.42%
combination therapy	endometrial cancer	142	33.81%	25	5.95%
	renal cell carcinoma	40	9.52%	7	1.67%
	hepatocellular carcinoma	39	9.29%	3	0.71%
	squamous cell carcinoma of head and neck	33	7.86%	11	2.62%
	clear cell renal cell carcinoma	24	5.71%	2	0.48%

haemorrhage, the largest ROR values were haemorrhagic tumour necrosis, tracheal haemorrhage, tumour haemorrhage. For pembrolizumab, the frequent adverse reaction signals comprised tumor haemorrhage, small intestinal haemorrhage, and enterocolitis haemorrhagic, with the highest ROR values linked to haemorrhagic stomatitis, tumor haemorrhage, and adrenal haemorrhage.

Given the ability of heat maps to visually illustrate differences in data across various groups, we employed the heatmap visualizes PT-level ROR values to compare haemorrhage risk profiles across treatment regimens (lenvatinib/pembrolizumab monotherapy, combination therapy). Lenvatinib alone exhibited the highest number of positive signals (31 positive signals), followed by combination therapy (20 positive signals) and pembrolizumab alone (10 positive signals). Further analysis of the therapy-related haemorrhage risk profile with different regimens at the PT level indicated that tumor haemorrhage, small intestinal haemorrhage, and tracheal haemorrhage were prevalent signals for lenvatinib alone, pembrolizumab alone, and combination therapy, as illustrated in Fig. 2. Noteworthy, the combination therapy exhibited some unique PTs, such as haemorrhagic stroke, renal haemorrhage, large intestinal haemorrhage, and stoma site haemorrhage, in comparison to lenvatinib and pembrolizumab alone.

Time to onset of haemorrhage

After excluding reports with erroneous, missing, or unclear reporting time at the time of onset, a total of 1066 bleeding events were used for time-to onset analysis, with 543 bleeding events in the lenvatinib alone, 263 bleeding events in the pembrolizumab alone and 260 bleeding events in the combination therapy, respectively. Figure 3 illustrates that the onset time of haemorrhage-related ADEs predominantly occurred within 1 month for lenvatinib alone, pembrolizumab alone, and combination therapy. The frequency of side effects declined over time, however haemorrhage-related ADEs can still appear a year after starting pembrolizumab and lentanib combination therapy. Notably, even after a year of treatment, our data suggest that continuous patient monitoring is required for possible side effects while on combination therapy with lenvatinib and pembrolizumab.

Drug-drug interaction analysis base on additive and multiplicative models

There were total of 38,416,055 ADEs were obtained from the FAERS database between 2015 Q1 and 2024 Q1, of which 43,623, 129,702, 19,865 were ADEs for lenvatinib alone, pembrolizumab alone and combination therapy, respectively. The results are shown in Table 4.

Since we wanted to compare the common suspicious bleeding signals in lenvatinib alone, pembrolizumab alone, and combination therapy, especially when combination therapy, therefore we chose the common suspicious bleeding signals of lenvatinib alone, pembrolizumab alone, and combination therapy. According to Fig. 2, it is evident that tumor haemorrhage, small intestinal haemorrhage, and tracheal haemorrhage were prevalent signals of haemorrhage-related ADEs for lenvatinib alone, pembrolizumab alone, and combination therapy. Consequently, an initial screening for common haemorrhage-related ADE signals and the risk of bleeding due to drug interactions through additive and multiplicative models is recommended. The signal detection outcomes are detailed in Table 5. According to the additive and multiplicative models, the Difference value > 0 (additive model) or Ratio values greater than 1 (multiplicative model) suggesting evidence of drug interaction.

Table 3 The haemorrhage signals on the PT level

PT	SOC	Freq	ROR(95%CI)	IC(IC025)
Lenvatinib				
Tumour haemorrhage	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	116	61.82(51.2-74.64)	5.85(4.18)
Cerebral haemorrhage	Nervous system disorders	114	4.83(4.01–5.8)	2.26(0.6)
Oesophageal varices haemorrhage	Gastrointestinal disorders	79	57.2(45.55–71.83)	5.75(4.08)
Upper gastrointestinal haemorrhage	Gastrointestinal disorders	43	3.33(2.47–4.49)	1.73(0.06)
Gastric haemorrhage	Gastrointestinal disorders	34	4.58(3.27–6.42)	2.19(0.52)
Arterial haemorrhage	Vascular disorders	31	39.6(27.63–56.77)	5.24(3.58)
Mouth haemorrhage	Gastrointestinal disorders	22	4.59(3.02–6.97)	2.19(0.52)
Tracheal haemorrhage	Injury, poisoning and procedural complications	20	101.74(64.03-161.65)	6.51(4.83)
Pulmonary haemorrhage	Respiratory, thoracic and mediastinal disorders	19	4.02(2.56–6.32)	2(0.34)
Duodenal ulcer haemorrhage	Gastrointestinal disorders	17	9.44(5.86–15.23)	3.23(1.56)
Haemobilia	Hepatobiliary disorders	17	60.57(37.05–99.01)	5.83(4.15)
Intra-abdominal haemorrhage	Gastrointestinal disorders	15	10.17(6.11–16.92)	3.33(1.66)
Gastric ulcer haemorrhage	Gastrointestinal disorders	14	4.06(2.4–6.86)	2.01(0.35)
Hepatic haemorrhage	Hepatobiliary disorders	12	25.26(14.23–44.84)	4.62(2.95)
Oesophageal haemorrhage	Gastrointestinal disorders	11	12.62(6.96–22.88)	3.64(1.97)
Cerebellar haemorrhage	Nervous system disorders	8	7.78(3.88–15.6)	2.95(1.28)
Diverticulum intestinal haemorrhagic	Gastrointestinal disorders	8	4.11(2.05–8.23)	2.03(0.37)
Adrenal haemorrhage	Endocrine disorders	6	16.44(7.33–36.88)	4.01(2.34)
Gastric varices haemorrhage	Gastrointestinal disorders	6	24.78(11.01–55.79)	4.59(2.92)
Thalamus haemorrhage	Nervous system disorders	6	8.71(3.9-19.47)	3.11(1.44)
Intracranial tumour haemorrhage	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	19.64(8.09–47.64)	4.27(2.59)
Small intestinal haemorrhage	Gastrointestinal disorders	5	3.64(1.51–8.77)	1.86(0.19)
Venous haemorrhage	Vascular disorders	4	16.84(6.26–45.28)	4.05(2.37)
Pharyngeal haemorrhage	Respiratory, thoracic and mediastinal disorders	4	4.69(1.75–12.52)	2.22(0.55)
Respiratory tract haemorrhage	Respiratory, thoracic and mediastinal disorders	4	9.05(3.38–24.22)	3.16(1.49)
Tongue haemorrhage	Gastrointestinal disorders	4	5.32(1.99–14.23)	2.41(0.74)
Haemorrhagic cerebral infarction	Nervous system disorders	3	7.78(2.5-24.26)	2.95(1.28)
Haemorrhagic tumour necrosis	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	131.95(39.21-444.08)	6.84(5.08)
Bronchial haemorrhage	Respiratory, thoracic and mediastinal disorders	3	12.45(3.98–38.91)	3.62(1.94)
Brain stem haemorrhage	Nervous system disorders	3	5.1(1.64–15.88)	2.34(0.67)
Putamen haemorrhage	Nervous system disorders	3	13.4(4.28–41.9)	3.72(2.05)
Pembrolizumab				
Tumour haemorrhage	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	66	11.43(8.94–14.62)	3.46(1.8)
Small intestinal haemorrhage	Gastrointestinal disorders	18	4.45(2.79–7.09)	2.14(0.47)
Enterocolitis haemorrhagic	Gastrointestinal disorders	12	4.62(2.61–8.18)	2.19(0.52)
Gastritis haemorrhagic	Gastrointestinal disorders	10	3.39(1.82–6.32)	1.75(0.08)
Adrenal haemorrhage	Endocrine disorders	6	5.52(2.46–12.37)	2.44(0.77)
Haemobilia	Hepatobiliary disorders	4	4.54(1.69–12.19)	2.17(0.49)
Tracheal haemorrhage	Injury, poisoning and procedural complications	3	4.66(1.49–14.58)	2.2(0.52)
Intracranial tumour haemorrhage	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	3.92(1.25–12.24)	1.96(0.28)
Stomatitis haemorrhagic	Gastrointestinal disorders	3	12.65(3.98–40.18)	3.61(1.91)
Spinal cord haemorrhage	Nervous system disorders	3	3.34(1.07–10.43)	1.73(0.05)
Combination therapy				
Cerebral haemorrhage	Nervous system disorders	41	3.8(2.79–5.16)	1.92(0.25)
Upper gastrointestinal haemorrhage	Gastrointestinal disorders	33	5.61(3.98–7.9)	2.48(0.82)
Tumour haemorrhage	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	31	34.49(24.17–49.21)	5.08(3.41)
Pulmonary haemorrhage	Respiratory, thoracic and mediastinal disorders	14	6.51(3.85-11)	2.7(1.03)
Haemorrhagic stroke	Nervous system disorders	14	5.56(3.29–9.4)	2.47(0.8)
Gastric haemorrhage	Gastrointestinal disorders	13	3.84(2.23–6.61)	1.94(0.27)
Subarachnoid haemorrhage	Nervous system disorders	11	3.42(1.9–6.19)	1.77(0.11)
Mouth haemorrhage	Gastrointestinal disorders	9	4.11(2.14–7.9)	2.04(0.37)
Oesophageal varices haemorrhage	Gastrointestinal disorders	6	8.99(4.03–20.06)	3.16(1.49)

Table 3 (continued)

PT	SOC	Freq	ROR(95%CI)	IC(IC025)
Renal haemorrhage	Renal and urinary disorders	5	7.59(3.15–18.26)	2.92(1.25)
Large intestinal haemorrhage	Gastrointestinal disorders	5	7.04(2.93–16.94)	2.81(1.14)
Small intestinal haemorrhage	Gastrointestinal disorders	5	8.01(3.33–19.28)	3(1.33)
Intra-abdominal haemorrhage	Gastrointestinal disorders	4	5.91(2.21–15.76)	2.56(0.89)
Oesophageal haemorrhage	Gastrointestinal disorders	3	7.48(2.41–23.25)	2.9(1.23)
Tracheal haemorrhage	Injury, poisoning and procedural complications	3	30.52(9.76–95.5)	4.91(3.23)
Pharyngeal haemorrhage	Respiratory, thoracic and mediastinal disorders	3	7.71(2.48–23.97)	2.94(1.27)
Stoma site haemorrhage	Injury, poisoning and procedural complications	3	4.6(1.48–14.29)	2.2(0.53)
Spinal cord haemorrhage	Nervous system disorders	3	21.88(7.01–68.3)	4.44(2.76)
Hepatic haemorrhage	Hepatobiliary disorders	3	13.58(4.36–42.28)	3.75(2.08)
Brain stem haemorrhage	Nervous system disorders	3	11.22(3.61–34.9)	3.48(1.81)

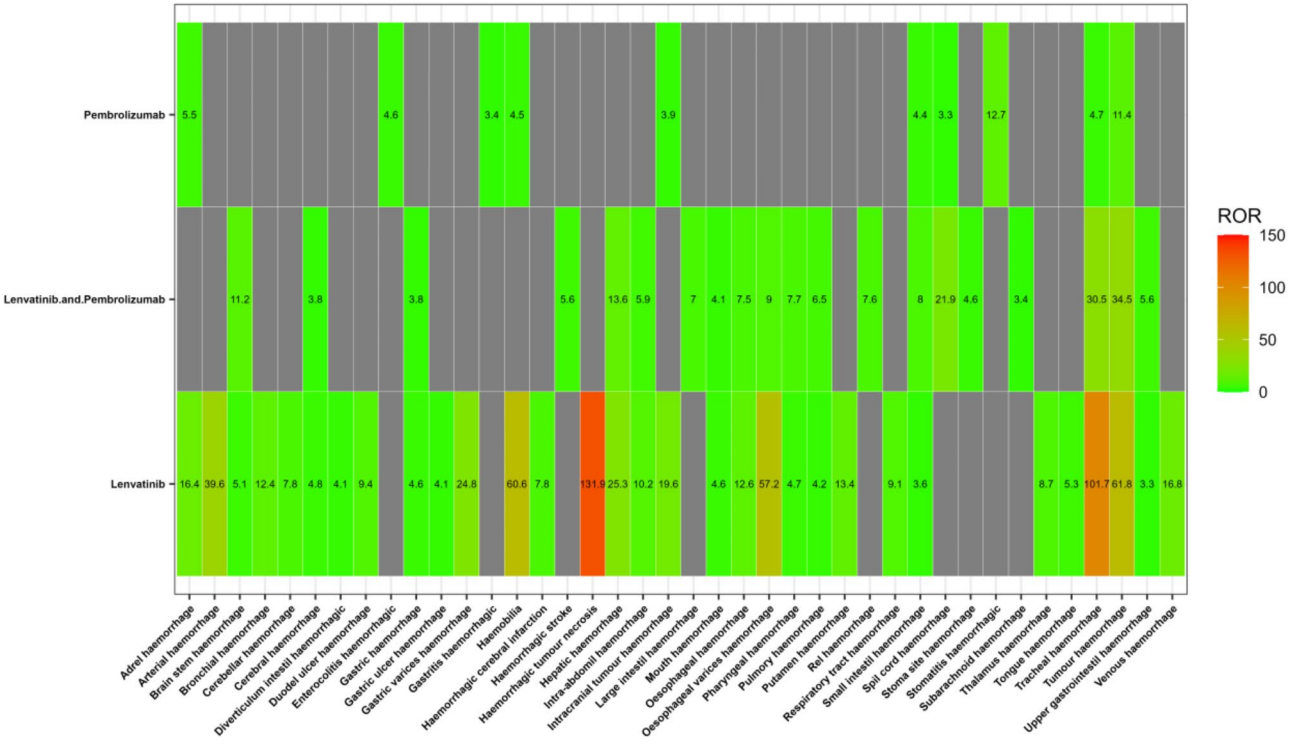

Fig. 2 Heat map of the risk of therapy-related bleeding risk profile with different regimens

Analysis revealed that the difference-ratio metrics for "Lenvatinib-Pembrolizumab-All haemorrhage ADE", "Lenvatinib-Pembrolizumab-Tumor haemorrhage", "Lenvatinib-Pembrolizumab-Small intestinal haemorrhage", and "Lenvatinib-Pembrolizumab-Tracheal haemorrhage" failed to satisfy the predefined positive interaction criteria (Difference > 0 and Ratio > 1). These results suggest that the combination of lenvatinib and pembrolizumab did not increase overall bleeding risk or specific bleeding events, consistent with the results of Phase III clinical trials [22].

Discussion

As lenvatinib and pembrolizumab is widely used in routine cancer treatment and monotherapy or combination with other agents, it will be especially important to recognize the risks of ADEs and intervene promptly to reduce its morbidity and mortality. Of all the common ADEs, bleeding events are frequently reported in clinical trials associated with lenvatinib and pembrolizumab [22, 23]. While phase 3 RCTs provide robust evidence on efficacy and safety, they often involve highly selected patient populations and controlled settings that may not fully reflect real-world clinical practice [24]. Considering the increasing use of lenvatinib in combination with pembrolizumab, ongoing pharmacovigilance monitoring

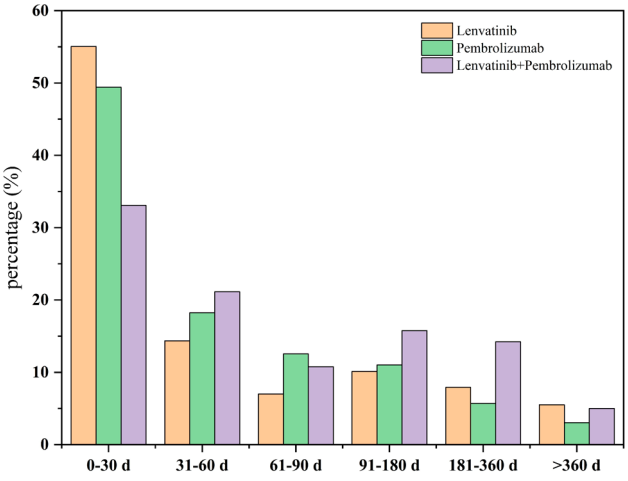

Fig. 3 The percentage of the onset time of haemorrhage reported in association with lenvatinib alone, pembrolizumab alone and combination therapy

is essential for clarifying the overall safety profile as well as providing comprehensive and accurate data to support public health and medical practice decision-making. Therefore, our study aims to complement RCT findings by providing real-world evidence on the incidence and risk factors for bleeding events in a broader patient population. In this study, we used the ROR, IC, additive and multiplicative models to detect possible signals of potential DDIs based on data from FAERS database. It is worth noting that the spontaneous reporting nature of the FAERS database may lead to reporting bias (e.g., selective reporting of serious events), thus affecting the reliability of risk signals. Therefore, although additive (risk difference) and multiplicative (relative risk) models are valuable for detecting potential drug-drug interaction (DDI) signals, they are exploratory tools that do not adjust for confounders (e.g., concomitant medications, disease severity). These modeling methods can detect disproportionate reporting signals, but unobserved confounders can bias risk estimates and are therefore not a substitute for multivariate adjustment. In the future, we need further validation in prospective studies.

To the best of our knowledge, this is the first comprehensive and methodical pharmacovigilance study utilizing the FAERS database to examine haemorrhagic signals associated with the co-administration of lenvatinib and pembrolizumab in a real-world setting. We discovered that the combination therapy of lenvatinib and pembrolizumab had a certain reduction in haemorrhagic risk when compared to the administration of lenvatinib alone, as confirmed by additive/multiplicative risk ratio approaches. According to the previous phase 3 clinical study, while combination therapy showed reduced overall haemorrhage risk compared to lenvatinib monotherapy, heterogeneity in baseline characteristics (e.g., cancer types, concomitant therapies) may confound comparisons. Clinicians still need to closely monitor the bleeding situation, especially those with bleeding risk factors, and timely manage and prevent the occurrence of bleeding complications [25].

Haemorrhage-related ADEs stemming from the co-administration of lenvatinib and pembrolizumab predominantly manifested in gastrointestinal, nervous system, respiratory, thoracic, and mediastinal issues, as well as injury, poisoning, and procedural complications. Notably, for nervous system disorders and gastrointestinal disorders, our findings offer a new supplementary evidence for the clinical application of these drugs from the pharmacovigilance perspective.

Lenvatinib combined with pembrolizumab: decreased overall haemorrhagic risk

Initially, with the exploration of emerging combination methodologies underway, it was observed that the documented incidence of haemorrhagic ADEs in the context

Table 4 Risk ratio of specific adverse events after the combination of lenvatinib and pembrolizumab

ADE	AGI and ICI	AGI, no ICI	no AGI, ICI	no AGI, no ICI
All haemorrhage ADE	420/19,865	1188/43,623	952/129,702	383,045/38,222,865
Tumour haemorrhage	31/19,865	116/43,623	66/129,702	1740/38,222,865
Small intestinal haemorrhage	5/19,865	5/43,623	18/129,702	1207/38,222,865
Tracheal haemorrhage	3/19,865	20/43,623	3/129,702	190/38,222,865

Table 5 Signal detection results for both the additive and multiplicative models

ADE	Additive model (α = 0.05)					Multiplicative model (α = 0.05)				
	RD_{AB}	RD_A+RD_B	Difference	δ	*P* value	RR_{AB}	RR_A+RR_B	Ratio	exp(δ)	*P* value
All haemorrhage ADE	0.01112	0.01453	-0.00341	0.0111	< 0.001	2.10977	1.99039	1.05998	2.1098	< 0.001
Tumour haemorrhage	0.00152	0.00308	-0.00156	0.0015	< 0.0001	34.28050	652.96169	0.05250	34.2813	< 0.0001
Small intestinal haemorrhage	0.00022	0.00019	2.9878E-05	0.0002	0.0505	7.97072	15.95189	0.49967	7.9709	< 0.0001
Tracheal haemorrhage	0.00015	0.00047	-0.00033	0.0001	0.0939	30.38102	429.16898	0.07079	30.3805	< 0.0001

Notes Difference = RD_{AB} - (RD_A + RD_B) > 0 (additive model) or Ratio = RR_{AB} / (RR_A × RR_B) > 1 (multiplicative model) suggests potential drug interaction signals. P-values assess statistical significance (α = 0.05)

of the co-administration of lenvatinib and pembrolizumab exhibited an annual increase from 2017 to 2023. Subsequently, the disproportionality analysis revealed that the signal strength of haemorrhagic ADEs, as indicated by IC025 or ROR025, was lower in individuals receiving the combination therapy of lenvatinib and pembrolizumab compared to those treated solely with lenvatinib, albeit notably higher than patients administered pembrolizumab alone. Our observation of haemorrhage risk in the combination therapy group (84.29% serious outcomes) aligns with the safety profile reported in the LEAP-002 trial (grade 3–4 bleeding events: ~5%) [22, 25], supporting the manageable safety of lenvatinib plus pembrolizumab in real-world settings. However, the higher proportion of severe events in FAERS likely reflects reporting bias toward serious adverse events rather than true risk differences. It should be noted that due to the strict control of confounding factors in phase 3 clinical study, it provides a high level of evidence for the safety of clinical treatment. In contrast to the phase 3 clinical study, our faers study is a retrospective study of the use of drugs in real-world populations. Although the study reflects a wider group of patients, it is observational and can only be used as supplementary evidence and cannot replace clinical trial data. Likewise, a pharmacovigilance investigation indicated that the joint use of lenvatinib and pembrolizumab resulted in diminished toxicity in comparison to lenvatinib monotherapy, potentially attributable to the reduced dosage of lenvatinib in the combined treatment regimen [26].

Variances in haemorrhage safety profiles of combination therapy

Multiple clinical trials indicated that the combination of lenvatinib and pembrolizumab maintained superior efficacy and manageable safety without new safety concerns compared to chemotherapy in previously treated advanced endometrial cancer patients [22, 25]. Compared with the clinical trials results, our study identified an overall reduction in haemorrhage risks with combination therapy compared to lenvatinib alone, it unveiled specific discrepancies in the haemorrhage safety profiles of the combined approach. Notably, in contrast to pembrolizumab used singularly, the combination therapy notably increased the risks of tumor haemorrhage, tracheal haemorrhage, spinal cord haemorrhage, and small intestinal haemorrhage based on specific PTs. However, the observed increased ROR may be due by unmeasured confounders (e.g. concomitant medication, patient baseline characteristics) or reporting bias, so the association of medication and bleeding events found in this study only reflects statistical signals and cannot be directly inferred as causality.

Additionally, when compared to lenvatinib or pembrolizumab treatment alone, combination therapy showed a decreased probability of haemorrhage beginning within a month. Therefore, clinicians should maintain vigilance for haemorrhage symptoms early in the course of lenvatinib-related therapy, particularly during the joint administration of lenvatinib and pembrolizumab. Although our research did not ascertain whether the risk of haemorrhage increased in a dose-dependent manner, continuous monitoring is essential throughout the treatment and post-treatment phases, as some cases of haemorrhage were reported long after the initiation of treatment. Haemorrhage-related ADEs were still evident beyond 360 days in over 5% of cases in both the singular use of lenvatinib and combination therapy. Meanwhile, scientific management requires a thorough understanding of the side effects of drug combinations. In the end, lowering the effective dosage is critical to lowering the frequency of undesirable outcomes rather than adding more medication to treat side effects. Personalized care requires close observation of the patient after administration.

Moreover, based on the heatmap analysis, we can know that tumour haemorrhage, small intestinal haemorrhage and tracheal haemorrhage is the common PTs for lenvatinib alone, pembrolizumab alone and combination therapy. These findings carry significant clinical relevance. In the context of cancer patients, tumor haemorrhage signifies the rupture of a blood vessel within the tumor or its infiltration into neighboring normal vessels [27]. This phenomenon is often attributed to the heightened demand for nutrients during malignant neoplasm progression, resulting in vascular rupture within the tumor tissue or invasion of adjacent normal vasculature as the tumor advances. Alterations in the tumor microenvironment also play a crucial role in precipitating tumor haemorrhage. By releasing several substances, such as VEGF, tumor cells promote angiogenesis, resulting in the formation of aberrant vascular structures that are intrinsically unstable and prone to rupture [28, 29]. Besides, lenvatinib's mechanism of action includes the induction of cell death in tumor cells, which can lead to necrosis and subsequent tissue damage. This necrotic process can engender vacant spaces and disrupt the structural integrity of normal tissue, potentially culminating in the formation of fistulas or direct haemorrhage from compromised vessels [16, 30]. Clinical reports have indicated that patients undergoing treatment with lenvatinib may develop complications like tracheal fistulas and haemorrhage due to necrotic changes in the surrounding tissues [31]. The incorporation of pembrolizumab in the treatment regimen may exacerbate these effects by modulating the immune milieu, resulting in heightened production of inflammatory cytokines that could further compromise vascular integrity [12, 32]. Research has indicated that

immune checkpoint inhibitors may influence the gut microbiota composition, leading to compromised gut barrier function and subsequent small intestinal haemorrhage [28, 29].

Given the propensity for tumor, small intestinal, and tracheal haemorrhage in patients receiving lenvatinib and pembrolizumab, meticulous monitoring and strategic management approaches are imperative. Clinicians should remain vigilant for haemorrhage-related signs and contemplate proactive measures such as imaging evaluations and therapeutic adjustments to mitigate this inherent risk. Moreover, a comprehensive comprehension of the underlying mechanisms can facilitate optimal patient selection and the formulation of supportive care strategies to enhance treatment safety.

New adverse reaction signals of combination therapy

Following the acquisition of all PT level ADE signals for lenvatinib and pembrolizumab administered individually, the signals were categorized based on their frequency and ROR, with a particular emphasis on gastrointestinal disorders. The higher the frequency, which is the greater the significance of the findings. After comparing with the PT of lenvatinib and pembrolizumab, it was found that combination therapy showed new ADE signals that were not mentioned in the lenvatinib and pembrolizumab.

Noteworthy new ADE signals associated with combination therapy included haemorrhagic stroke (ROR 5.56, IC 2.47), renal haemorrhage (ROR 7.59, IC 2.92), large intestinal haemorrhage (ROR 7.04, IC 2.81), and stoma site haemorrhage (ROR 4.6, IC 2.2). Notably, renal haemorrhage (ROR 7.59, IC 2.92) exhibited high frequency and a robust signal, prompting heightened vigilance towards this adverse reaction during the administration of the combination therapy. Hence, when contemplating combination therapy, a comprehensive assessment of the clinical benefits and potential novel adverse effects associated with the medication in question is imperative.

Baseline model validation of drug-drug interactions

The baseline model comprises both an additive and a multiplicative model. Both models facilitate the swift and efficient detection of DDIs signals, thereby fostering the enhancement of judicious clinical drug utilization [33]. The additive model enhances extant signal detection methodologies by virtue of its heightened sensitivity, enabling the identification of a greater number of suspicious signals. While the multiplicative model's reliability can be fortified, its sensitivity is constrained by the volume of event reports and ratio computation, resulting in a diminished signal detection rate. Employing pertinent statistical tests can augment the precision of signal detection [20]. Consequently, we utilized a baseline model to scrutinize the specific PTs (tumour haemorrhage, small intestinal haemorrhage, tracheal haemorrhage) associated with individual administrations of lenvatinib and pembrolizumab, as well as their combination therapy, to ascertain if the combined regimen escalated the incidence of bleeding adverse events. In this study, the amalgamation of "Lenvatinib-Pembrolizumab-small intestinal haemorrhage" exhibited a discrepancy of 2.9878E-05 in the additive model, indicative of a positive interaction (> 0). However, the sparsity of data or the lack of key variables (e.g., dose, treatment duration) may affect the accuracy and cannot prove their causal relationship. The specific clinical significance of this needs to be verified by prospective trials. Hence, during the signal detection process, when the additive model initially yields affirmative outcomes, vigilance is imperative regarding potential adverse drug reactions in combination regimens, necessitating the conduction of pertinent statistical analyses to elucidate the presence of drug interactions.

DDIs is one of the main causes of adverse reactions. With the rise in multi-drug usage, timely identification of DDIs is critical for clinical applications, pharmacovigilance, and protection of patient health [34]. The primary value of this study resides in evaluating the safety of co-administering lenvatinib with pembrolizumab based on real-world data. Moreover, the study employs the ROR, IC, additive and multiplicative models to rigorously assess the consistency and robustness of the findings, thereby empowering clinicians to make more informed therapeutic decisions, particularly when confronted with the challenge of selecting between these two agents.

In essence, it is posited that combination therapy reduces the risk of some serious haemorrhage side effects while simultaneously increasing the effectiveness of anti-tumor treatment. However, before starting combination therapy, it is crucial to thoroughly assess the drugs' potential overlapping toxicities as well as their clinical benefits. Moreover, further research to corroborate our findings is highly recommended.

Limitations

There are a few intrinsic limitations to consider. First of all, the FAERS database is a self-reporting system that has some reporting bias (e.g., missing gender and age information) and intrinsic reporting unpredictability (e.g., incomplete, erroneous, selective, delayed, and unverified reporting). Additionally, it is tough to account for the lack of granular data like as cancer stage, dosage, amount of usage, comorbidities, and other influences on the occurrence of haemorrhage-related side events. The inability to adjust for absence of key clinical variables (e.g., cancer stage, dose variations, comorbidities) may influence risk comparisons. We precluded sensitivity analyses to validate robustness. Future studies integrating structured electronic health records are warranted to address

confounding. Thus, findings should be interpreted cautiously. Second, because the US FDA maintains the database, it inherently lacks cases from other nations and could add bias by limiting analyses to particular regions due to varying priorities on adverse occurrences in different nations and regions [35]. It is crucial to acknowledge that biases in this research are inevitable and cannot be completely eradicated. Thirdly, the incidence of adverse events related with the combination of pembrolizumab and lenvatinib could not be calculated because there was no population base dedicated to this particular medication. Ultimately, the signals uncovered by data mining do not establish a causative relationship; rather, they just show a correlation between a medicine and an adverse occurrence. They can therefore only be used to generate hypotheses and not for certification. Therefore, to establish whether a biological causal relationship exists, more clinical follow-up, observational, and pharmacological research are required. Our findings are limited to statistical correlations. Despite these drawbacks, our results can provide guidance for further research, and healthcare professionals can use this article as a useful resource to track adverse events linked to haemorrhage that are connected to the combination of lenvatinib and pembrolizumab.

Conclusion

This study offers the large-scale real-world evidence on haemorrhage risks associated with lenvatinib-pembrolizumab combination therapy, complementing RCT data to build a comprehensive safety profile. We observed that the combination of lenvatinib and pembrolizumab mitigates certain severe haemorrhage ADEs compare with lenvatinib alone, but we also found combination therapy showed new ADE signals that were not mentioned in the lenvatinib and pembrolizumab. These results indicated that in order to validate these findings and ascertain the connections between them, prospective clinical trials are required. In summary, this study offers more details about the safety profile of lenvatinib and pembrolizumab combined in clinical settings. It may also help physicians choose the right treatments, enhance patient safety, and improve treatment outcomes for patients on lenvatinib + pembrolizumab.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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This study was conducted using the FDA Adverse Event Reporting System (FAERS) database provided by the FDA. The information, findings, and interpretations in this study do not represent the views of the FDA.

Author contributions
SQ.W. and GZ.R. wrote the main manuscript text and H.P, JY.C, JY.H prepared figures and TABLE. ZZ.L, QH.M and GS.Z collaborated in the study development and critically revised the manuscript. All authors reviewed the manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files. The original data could be obtained from FAERS (https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html). This manuscript contains data presented as electronic supplementary material.

Declarations

Ethical approval
The FAERS database contains anonymized patient information. The Hospital Ethics Committee has confirmed that ethical approval was not required.

Consent to participate
Not applicable because spontaneous reports of the FAERS are anonymous and publicly available.

Consent for publication
Not applicable because spontaneous reports of the FAERS are anonymous and publicly available.

Competing interests
The authors declare no competing interests.

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