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ORIGINAL RESEARCH

Investigating Drug-Induced Thyroid Dysfunction Adverse Events Associated With Non-Selective RET Multi-Kinase Inhibitors: A Pharmacovigilance Analysis Utilizing FDA Adverse Event Reporting System Data

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Purpose: This study aims to investigate the potential association between non-selective RET kinase inhibitors and thyroid dysfunction (TD) by conducting a pharmacovigilance analysis using data from the US FDA Adverse Event Reporting System (FAERS).

Methods: Data for non-selective RET MKIs were obtained from the FAERS database, spanning the first quarter of 2015 to the fourth quarter of 2023. Disproportionality analysis was used to quantify the AE signals associated with non-selective RET MKIs and to identify TD AEs. Subgroup analyses and multivariate logistic regressions were used to assess the factors influencing the occurrence of TD AEs. Time-to-onset (TTO) analysis and the Weibull Shape Parameter (WSP) test were also performed.

Results: Descriptive analysis revealed an increasing trend in TD adverse events linked to non-selective RET MKIs, with a notable proportion of serious reactions reported. Disproportionality analysis using ROR, PRR, BCPNN, and EBGM algorithms consistently demonstrated a positive association between Sunitinib, Cabozantinib, and Lenvatinib with TD adverse events. Subgroup analyses highlighted differential susceptibility to TD based on age, gender, and weight, with varying patterns observed for each inhibitor. Logistic regression analyses identified factors independently influencing the occurrence of TD adverse events, emphasizing the importance of age, gender, and weight in patient stratification. Time-to-onset analysis indicated early manifestation of TD adverse events following treatment with non-selective RET MKIs, with a decreasing risk over time.

Conclusion: The results of our study indicate a correlation between the use of non-selective RET MKIs and the occurrence of TD AEs. This may provide support for the clinical monitoring and risk identification of non-selective RET MKIs. Nevertheless, further clinical studies are required to substantiate the findings of this study.

Keywords: drug-induced thyroid dysfunction, non-selective RET MKIs, pharmacovigilance, FDA adverse event reporting system, clinical monitoring

Introduction

RET is a proto-oncogene that encodes a tyrosine kinase receptor and plays a key role in regulating physiological processes such as cell proliferation and differentiation. Fusion rearrangement of RET with other genes can lead to the formation of abnormal RET fusion proteins. The protein exhibits enhanced kinase activity, blocked signal transduction, increased cell proliferation, and other characteristics, resulting in abnormal proliferation and dissemination of tumor cells

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[2,3.] Based on these properties, RET has become an important drug target in cancer treatment. Since the functional domains and ATP binding sites of RET and other receptor tyrosine kinases (RTKs) are similar in structure, some small molecule multikinase inhibitors (MKIs) can inhibit RET activity, which has been applied in clinical practice. Several MKIs have received FDA approval for cancer therapy, including Sunitinib, Sorafenib, Vandetanib, Cabozantinib, and Lenvatinib. [3.]

Although numerous patients have benefit from RET MKIs, drug-related toxicity cannot be ignored. RET MKIs have poor specificity, they can target not only RET but also other kinases such as EGFR, human epidermal growth factor receptor-2 (HER-2), VEGFR2, etc, resulting in off-target toxicity and causing a high incidence of adverse events (AEs).[5,6] The occurrence of AEs may lead to the reduction or termination of non-selective RET MKIs treatment. It is very important for the prognosis of patients to recognize AEs and deal with them in time. The thyroid gland is the largest endocrine organ in the human body, consisting of two connected lobes, with an average weight of approximately 20–30 grams in adults. Thyroid lesions are relatively common in the general population, with a prevalence of 4% to 7%. Most of these lesions are asymptomatic, with normal secretion of thyroid hormones.[7] Thyroid dysfunction (TD) is one of the adverse events of RET kinase inhibitors, defined as thyroid hormone levels (thyroxine [T4] and triiodothyronine [T3]) greater than or less than the reference range. TD is a common pathological state of thyroid hormone disorders, which is associated with an increased risk of cardiac arrhythmias, atherosclerotic vascular disease, and heart failure (HF). It has also been associated with a higher risk of premature morbidity and death as well as with an increased incidence of CV risk factors such as hypertension, diabetes, and dyslipidemia. TD seriously affects the quality of life of patients and may even lead to death.[9,10] Studies have shown that 57% of patients have elevated thyroid stimulating hormone (TSH) levels after receiving Cabozantinib treatment.[11,12] After a follow-up of 66 patients treated with Sunitinib at the Taussig Cancer Center of the Cleveland Clinic, 56 of them showed hypothyroidism. A similar situation occurred in patients receiving Sorafenib treatment.[14,15]

However, there is still a lack of comprehensive research on thyroid-related adverse events caused by non-selective RET MKIs. Furthermore, it should be noted that TD AEs were not even listed on drug labels with the exception of the labels of Sunitinib and Lenvatinib. Therefore, the toxicities of TD may be underestimated in the clinical practice of these inhibitors. The US Food and Drug Administration Adverse Event Reporting System (FAERS) is a vast database that contains a wide range of real-world data to the FDA, including drug details, sources, therapies, demographics, indications, adverse reactions, and outcomes.[16] The data recorded were submitted worldwide.[16] The huge FAERS data submitted from the real world make it valuable in the identification of new and rare signals. This study thoroughly examines the association between the clinical application of non-selective RET MKIs and the occurrence of TD events by utilizing standardized data within FAERS, offering valuable insights for the administration of these inhibitors.

Methods

Data Source

We conducted this pharmacovigilance study of non-selective RET MKIs-related thyroid dysfunction using the data covering from the quarterly data extraction files of FAERS (available for download at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html) database. The study design is shown in Figure 1.

In our retrospective analysis, the data were extracted from FAERS spanning the period from the first quarter of 2015 to the fourth quarter of 2023. To ensure data integrity, we meticulously deduplicated multiple instances of the same report before commencing statistical analysis. Specifically, we removed duplicates based on matching "CASEID" values and prioritized reports with the most recent "FDA_DT" (date FDA received case) for cases sharing the same "CASEID." Additionally, we streamlined the association between drugs and AEs by assigning the role code as primary suspected (PS) only. Any missing data were designated as "unknown" to maintain data consistency.

We identified all reports related to non-selective RET MKIs by cross-referencing generic names (drug name and prod_ai columns) and trade names (drug name column) in the DRUG file, including Lenvatinib (Lenvima), Vandetanib (Caprelsa, Zactima), Cabozantinib (Cometriq), Sunitinib (Sutent), and Sorafenib (Nexavar). Statistical tests were

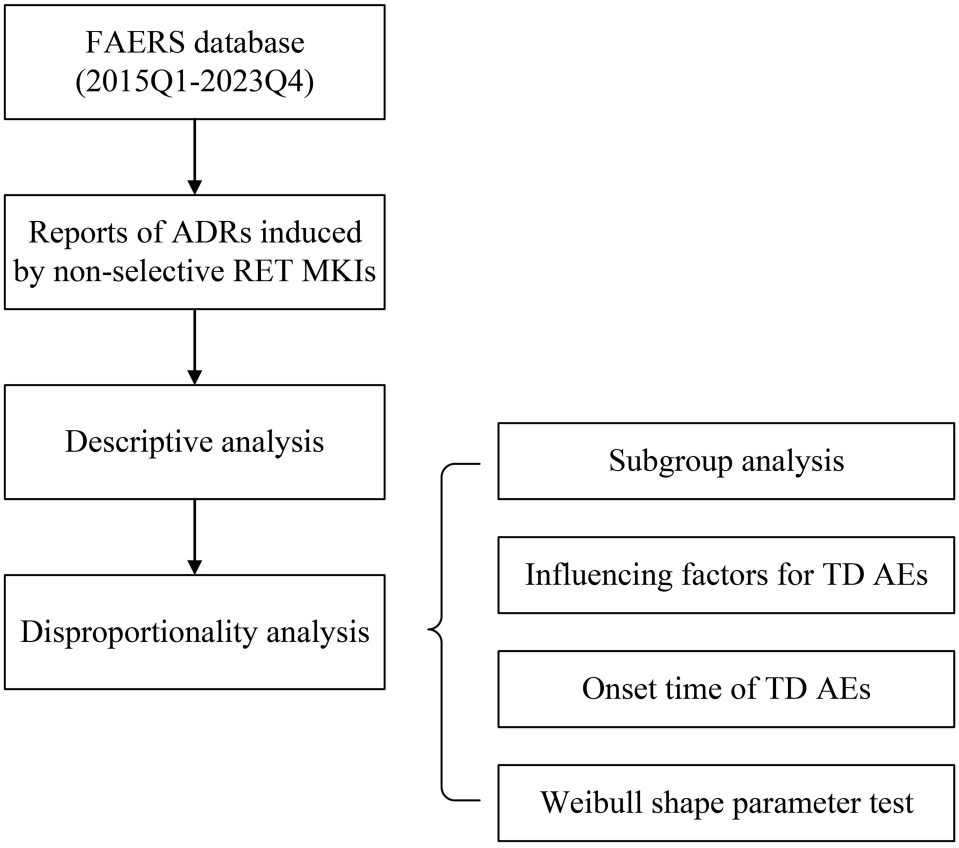

Figure 1 The process of data extraction, processing, and analysis from the FAERS database.

conducted using a two-tailed approach, with a statistical significance set at $p < 0.05$. Data processing and statistical analyses were carried out using Microsoft Excel 2021 and R software (version 4.3.2) to ensure robust analysis.

Identification of Target AE Report

The FAERS database employs the Medical Dictionary for Regulatory Activities (MedDRA) to standardize the encoding of various adverse drug reaction (ADR) information into Preferred Terms (PTs). Standardized MedDRA Queries (SMQs) within MedDRA facilitate the retrieval of relevant cases and optimize ADR signal detection and evaluation by grouping similar medical conditions. SMQs offer two search options: broad-scope search, encompassing comprehensive PTs, and narrow-scope search, focusing on closely related PTs. This study, following MedDRA version 26.0, selectively utilizes PTs from the narrow-scope search "Thyroid dysfunction (SMQ)" to ascertain the target AE report (refer to Table 1). The identification of the target report involves cross-referencing PTs from Table 1 with the "patient.reaction.reactionmeddrapt" field of the AE report.

Signal Mining

The proportional disequilibrium method and Bayesian method are critical analytical tools utilized in the field of pharmacovigilance. The proportional disequilibrium method involves a comparison of the occurrence proportions of adverse events between a target drug and all other drugs. This analysis encompasses both the reported odds ratio (ROR) and the proportional reported odds ratio (PRR).[18,19] On the other hand, the Bayesian method incorporates two prominent algorithms: the Bayesian confidence propagation neural network (BCPNN) and the multiple Gamma Poisson reduction method (EBGM).[20,21] To enhance the credibility of the correlation analysis between drugs and adverse events, this study employed four distinct algorithms: ROR, PRR, BCPNN, and EBGM. These algorithms were all employed to quantify the correlation between non-selective RET MKIs and thyroid dysfunction. Drawing from the four-cell table of the ratio imbalance method (Table 2), as well as the Bayesian method, the formulas and signal detection criteria for these four algorithms were delineated in Table 2.

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Table 1 The List of Thyroid Dysfunction Adverse Events Analyzed in This Study

AUTOIMMUNE HYPOTHYROIDISM
BASEDOW'S DISEASE
TERTIARY HYPOTHYROIDISM
CENTRAL HYPOTHYROIDISM
SECONDARY HYPOTHYROIDISM
CONGENITAL HYPOTHYROIDISM
ENDOCRINE OPHTHALMOPATHY
EXOPHTHALMOS
GENERALISED RESISTANCE TO THYROID HORMONE
HASHITOXICOSIS
HYPERTHYROIDISM
HYPOTHYROIDIC GOITRE
HYPOTHYROIDISM
IMMUNE-MEDIATED HYPERTHYROIDISM
IMMUNE-MEDIATED HYPOTHYROIDISM
INAPPROPRIATE THYROID STIMULATING HORMONE SECRETION
MARINE LENHART SYNDROME
MYXOEDEMA
MYXOEDEMA COMA
POST PROCEDURAL HYPOTHYROIDISM
HYPOTHYROIDISM POSTOPERATIVE
PRIMARY HYPERTHYROIDISM
PRIMARY HYPOTHYROIDISM
SECONDARY HYPERTHYROIDISM
THYROID ATROPHY
THYROID DERMATOPATHY
THYROID STIMULATING HORMONE DEFICIENCY
THYROID TUBERCULOSIS
THYROTOXIC CARDIOMYOPATHY
THYROTOXIC CRISIS
THYROTOXIC MYOPATHY
THYROTOXIC PERIODIC PARALYSIS
TOXIC GOITRE
TOXIC NODULAR GOITRE

Table 2 Formulas and Signal Detection Standards of ROR, PRR, BCPNN, and EBGM

Algorithms	Formulas	Standards
ROR	$\mathrm{ROR} = \frac{ad}{bc}$ $95\%\mathrm{CI} = e^{\ln(ROR)\pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$	a≥3, the lower limit of 95% CI>1
PRR	$\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$ $95\%\mathrm{CI} = e^{\ln(PRR)\pm 1.96\sqrt{\left(\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}\right)}}$	a≥3, the lower limit of 95% CI>1
BCPNN	$IC = log_2\frac{p(x,y)}{p(x)p(y)} = log_2\frac{a(a+b+c+d)}{(a+b)(a+c)}$ $E(IC) = log2\frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$ $V(IC) = \frac{1}{(ln2)^2}\left\{\begin{array}{l}\left[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)}\right] \\ +\left[\frac{(a+b+c+d)-(a+b)+\alpha-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)}\right] \\ +\left[\frac{(a+b+c+d)-(a+c)+\beta-\beta 1}{(a+c+\beta 1)(1+a+b+c+d+\beta)}\right]\end{array}\right\}$ $\gamma = \gamma 11\frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$ $IC - 2SD = E(IC) - 2\sqrt{V(IV)}$ $\alpha 1 = \beta 1 = 1,\ \alpha = \beta = 2,\ \gamma 11 = 1$	a≥3, IC025>0
EBMG	$EBGM = \frac{a(a+b+c+d)}{(a+c)(a+b)}$, $EBGM05 = e^{\ln(EBGM)-1.64\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)^{0.5}}$	a>0, EBGM05>2

Equation: a, the number of reports simultaneously containing the target drug and target adverse events; b, the number of reports simultaneously containing the target drug and other adverse events; c, the number of reports simultaneously containing the other drugs and target adverse events; d, number of reports simultaneously containing the other drugs and the other adverse events.

Time-To-onset Analysis and Sensitivity Analysis

Time-to-onset (TTO) was calculated as the duration between the date of adverse events (EVENT_DT in the DEMO file) and the initiation of MKI treatment (START_DT in the THER file).[22] Only reports with available TTO data were included in the analysis, with reports containing input errors (EVENT_DT occurring before START_DT) being excluded beforehand to ensure calculation accuracy. The incidence of adverse events may fluctuate over time. To evaluate whether the rate of adverse events changes with time, we conducted the Weibull Shape Parameter (WSP) test.[23,24] The Weibull distribution is utilized as a probability distribution for characterizing reliability and lifetime data, with the scale parameter α and shape parameter β defining the distribution. Initially, we determined the median time to onset of adverse events using the formula: Time-to-onset (TTO) = Event time (EVENT_DT in DEMO file) − Start time (START_DT in THER file). The results of the WSP test indicate three hazard models: wear-out failure type, suggesting an increasing risk of adverse events over time ($\beta > 1$, 95% CI > 1); early failure type, indicating a decreasing risk of adverse events over time ($\beta < 1$, 95% CI < 1); random failure type, depicting a constant or stable risk of adverse events over time (β equal to or near 1, 95% CI encompassing the value 1).

Causality Assessment

Austin Bradford-Hill criteria, which were proposed by Sir Austin Bradford-Hill, have been used broadly in pharmacoepidemiology and are also relevant to pharmacovigilance.[25] Using the updated criteria,[26] we systematically collected evidence for Sunitinib, Cabozantinib, and Lenvatinib-related TD AEs, and initially assessed the causality on the basis of evidence.

Results

Descriptive Analysis of TD AEs in Non-Selective RET MKIs Patients

Initially, we examined the occurrence of TD AEs in patients receiving non-selective RET multikinase inhibitors in FAERS from the first quarter of 2015 to the fourth quarter of 2023, with detailed data processing outlined in Figure 1. Across the 9 years, FAERS contained 12,632,257 cases, of which 74,937 were associated with non-selective RET MKI use (8,177 for Sorafenib, 18,906 for Sunitinib, 808 for Vandetanib, 27,938 for Cabozantinib, and 19,108 for Lenvatinib)

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as depicted in Figure 2A. Among these cases, 1,655 were linked to adverse thyroid function events, representing 2.21% (1,655/74,937) of the total cases. While the frequency of non-selective RET MKIs-related reports remained modest biennially, there was a general upward trend observed in this proportion (Figure 2B).

The clinical features of thyroid dysfunction adverse events associated with non-selective RET MKIs are detailed in Figure 3 and Table 3. While the number of cases showed a general annual increase, it was declined slightly in 2020 (Figure 3A). This trend may plausibly be linked to the global impact of the COVID-19 pandemic. The pandemic caused significant disruptions in healthcare systems worldwide, including delays in non-emergency medical visits, interruptions in routine monitoring, and changes in treatment protocols. Additionally, reduced reporting rates to pharmacovigilance systems during this period might have influenced the observed decline. Males surpassed females in representation (49.10% versus 43.40%) among all cases (Figure 3B). Notably, males treated with Sorafenib, Sunitinib, Vandetanib, and Cabozantinib exhibited a higher susceptibility to thyroid dysfunction compared to females. Conversely, males receiving Lenvatinib showed a lower propensity for thyroid dysfunction than females (34.60% versus 63.00%). Patient age primarily ranged from 18 to 65 years (Figure 3C), with most individuals weighing between 50kg and 100kg (Figure 3D). Physicians constituted the majority of reporters (67.90%) (Figure 3E). The top five countries with the highest reporting frequency were Japan, the United States of America, Poland, France, and Italy (Figure 3F). Among the 1,655 cases of thyroid dysfunction adverse events linked to non-selective RET multikinase inhibitors, a significant proportion (79.27%, 1,312/1,655) were classified as "serious" reactions, involving instances such as death (148 cases), life-threatening events (39 cases), disabilities (8 cases), initial or prolonged hospitalizations (528 cases), interventions to prevent permanent harm (1 case), and other serious medical events (588 cases). Among the 148 death-related cases, 7 were attributed to Sorafenib, 39 to Sunitinib, 1 to Vandetanib, 42 to Cabozantinib, and 59 to Lenvatinib (Table 3).

Disproportionality Analysis

Four algorithms, including ROR, PRR, BCPNN, and EBGM, were employed to assess the correlation between the usage of non-selective RET multikinase inhibitors and thyroid dysfunction (TD). All these algorithms consistently signaled a positive association between non-selective RET MKIs and TD based on their respective signal detection criteria (refer to Table 4). Further evaluation revealed that Sunitinib, Cabozantinib, and Lenvatinib consistently displayed positive signals for TD, with varying signal intensities: Sunitinib exhibited the lowest intensity and Lenvatinib the highest (Table 4). Conversely, Sorafenib and Vandetanib showed no significant correlation with TD (Table 4). Consequently, the study primarily focused on Sunitinib, Cabozantinib, and Lenvatinib, which demonstrated significant associations with TD. The Preferred Terms (PTs) for all TD adverse events underwent disproportionality analysis utilizing the entire FAERS database as a reference. Following the identification of valid signals, the analysis revealed distinct TD adverse events associated with the three non-selective RET MKIs (Table 5). Among these, "HYPOTHYROIDISM" exhibited the highest number of cases and the most pronounced signal intensity (Table 5).

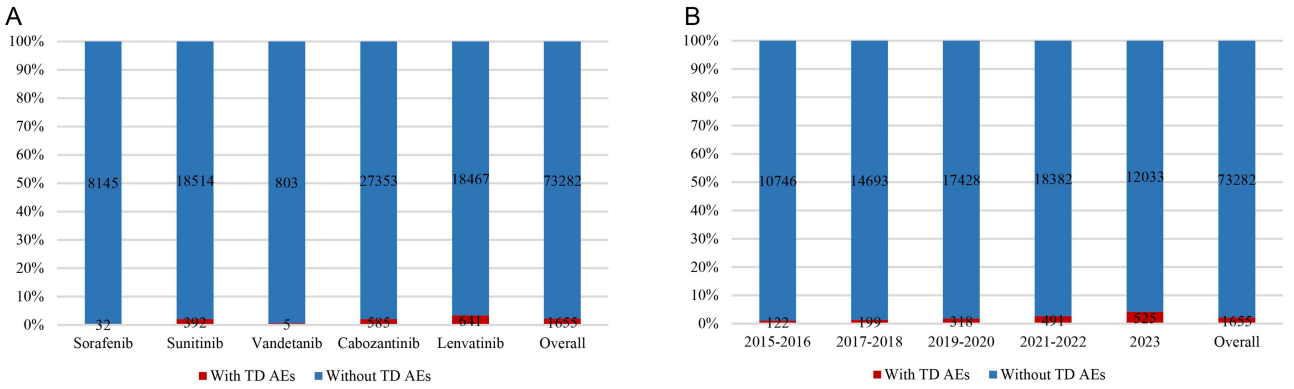

Figure 2 Statistics on the reporting rate of TD adverse events (AEs) associated with non-selective RET MKIs in the FAERS database from the first quarter of 2015 to the fourth quarter of 2023 are analyzed. This analysis includes (**A**) a comparison between the reported cases of non-selective RET MKIs-related AEs with and without TD, and (**B**) a comparison between the reported cases of TD adverse events and non-TD adverse events associated with non-selective RET MKIs in FAERS from 2015 to 2023.

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Figure 3 Basic information of TD AEs associated with non-selective RET MKIs in the FAERS database from 2015Q1 to 2023Q4. (**A**) The number of annual TD AEs. (**B**) The distribution of gender. (**C**) The distribution of age. (**D**) The distribution of weight. (**E**) The distribution of reporters. (**F**) The top 5 countries reported the highest number of TD AEs. (**G**) The distribution of outcomes.

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Table 3 The Clinical Characteristics of Thyroid Dysfunction Adverse Events Associated With the Five Non-Selective RET MKIs

Characteristics		Sorafenib (n, %)	Sunitinib (n, %)	Vandetanib (n, %)	Cabozantinib (n, %)	Lenvatinib (n, %)	In total (n, %)
Gender	Male	18 (56.3%)	207 (52.8%)	4 (80.0%)	362 (61.9%)	222 (34.6%)	813 (49.1%)
	Female	14 (43.8%)	153 (39.0%)	1 (20.0%)	146 (25.0%)	404 (63.0%)	718 (43.4%)
	Unknown	0 (0%)	32 (8.2%)	0 (0%)	77 (13.2%)	15 (2.3%)	124 (7.5%)
Age	<18	1 (3.1%)	5 (1.3%)	0 (0%)	8 (1.4%)	2 (0.3%)	16 (1.0%)
	18≤and<65	15 (46.9%)	188 (48.0%)	1 (20.0%)	152 (26.0%)	174 (27.1%)	530 (32.0%)
	65≤and≤85	12 (37.5%)	145 (37.0%)	3 (60.0%)	197 (33.7%)	273 (42.6%)	630 (38.1%)
	>85	1 (3.1%)	0 (0%)	0 (0%)	6 (1.0%)	8 (1.2%)	15 (0.9%)
	Unknown	3 (9.4%)	54 (13.8%)	1 (20.0%)	222 (37.9%)	184 (28.7%)	464 (28.0%)
Weight	<50 kg	1 (3.1%)	7 (1.8%)	0 (0%)	15 (2.6%)	41 (6.4%)	64 (3.9%)
	50~100 kg	1 (3.1%)	113 (28.8%)	1 (20.0%)	100 (17.1%)	164 (25.6%)	379 (22.9%)
	>100 kg	0 (0%)	13 (3.3%)	0 (0%)	4 (0.7%)	5 (0.8%)	22 (1.3%)
	Unknown	30 (93.8%)	259 (66.1%)	4 (80.0%)	466 (79.7%)	431 (67.2%)	1190 (71.9%)
Reporter	Consumer	11 (34.4%)	85 (21.7%)	1 (20.0%)	91 (15.6%)	45 (7.0%)	233 (14.1%)
	Health Professional	7 (21.9%)	20 (5.1%)	0 (0%)	41 (7.0%)	39 (6.1%)	107 (6.5%)
	Physician	8 (25.0%)	206 (52.6%)	3 (60.0%)	408 (69.7%)	499 (77.8%)	1124 (67.9%)
	Other health-professional	6 (18.8%)	43 (11.0%)	0 (0%)	16 (2.7%)	2 (0.3%)	67 (4.0%)
	Pharmacist	0 (0%)	37 (9.4%)	1 (20.0%)	29 (5.0%)	55 (8.6%)	122 (7.4%)
	Unknown	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)	1 (0.2%)	2 (0.1%)
Country (top five)	Japan	7 (21.9%)	49 (12.5%)	0 (0%)	269 (46.0%)	464 (72.4%)	789 (47.7%)
	United States of America	2 (6.3%)	91 (23.2%)	2 (40.0%)	113 (19.3%)	73 (11.4%)	281 (17%)
	Poland	0 (0%)	44 (11.2%)	0 (0%)	35 (6.0%)	2 (0.3%)	81 (4.9%)
	France	2 (6.3%)	26 (6.6%)	1 (20.0%)	41 (7.0%)	10 (1.6%)	80 (4.8%)
	Italy	1 (3.1%)	9 (2.3%)	1 (20.0%)	24 (4.1%)	7 (1.1%)	42 (2.5%)

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Outcome	Death	7 (21.88%)	39 (9.95%)	1 (20%)	42 (7.18%)	59 (9.2%)	148 (8.94%)
	Life-Threatening	0 (0%)	8 (2.04%)	0 (0%)	15 (2.56%)	16 (2.5%)	39 (2.36%)
	Disability	0 (0%)	0 (0%)	0 (0%)	4 (0.68%)	4 (0.62%)	8 (0.48%)
	Hospitalization - Initial or Prolonged	8 (25%)	110 (28.06%)	0 (0%)	101 (17.26%)	309 (48.21%)	528 (31.9%)
	Required Intervention to Prevent Permanent Impairment/Damage	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.16%)	1 (0.06%)
	Other Serious (Important Medical Event)	17 (53.13%)	203 (51.79%)	2 (40%)	244 (41.71%)	122 (19.03%)	588 (35.53%)
	Nonserious outcome	0 (0%)	32 (8.16%)	2 (40%)	179 (30.6%)	130 (20.28%)	343 (20.73%)
Year	2015	0 (0%)	57 (14.5%)	1 (20.0%)	2 (0.3%)	0 (0%)	60 (3.6%)
	2016	5 (15.6%)	55 (14.0%)	0 (0%)	2 (0.3%)	0 (0%)	62 (3.7%)
	2017	4 (12.5%)	52 (13.3%)	0 (0%)	14 (2.4%)	3 (0.5%)	73 (4.4%)
	2018	6 (18.8%)	61 (15.6%)	0 (0%)	20 (3.4%)	39 (6.1%)	126 (7.6%)
	2019	2 (6.3%)	41 (10.5%)	1 (20.0%)	49 (8.4%)	72 (11.2%)	165 (10.0%)
	2020	8 (25.0%)	38 (9.7%)	0 (0%)	48 (8.2%)	59 (9.2%)	153 (9.2%)
	2021	3 (9.4%)	39 (9.9%)	0 (0%)	92 (15.7%)	42 (6.6%)	176 (10.6%)
	2022	4 (12.5%)	25 (6.4%)	2 (40.0%)	150 (25.6%)	134 (20.9%)	315 (19.0%)
	2023	0 (0%)	24 (6.1%)	1 (20.0%)	208 (35.6%)	292 (45.6%)	525 (31.7%)

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Table 4 Counts of TD AEs With Associated ROR, PRR, EBGM, and BCPNN for Non-Selective RET MKIs From the FAERS Database

Drug	N	ROR (95% CI)	PRR (95% CI)	EBGM05	BCPNN (IC025)	P
Sorafenib	32	1.00 (0.71–1.41)	1.00 (0.65–1.34)	0.75	−1.67	1
Sunitinib	409	6.12 (5.55–6.74)	6.09 (5.99–6.16)	5.55	0.92	0
Vandetanib	5	1.85 (0.77–4.44)	1.84 (0.97–2.72)	0.89	−0.78	0.28
Cabozantinib	607	7.37 (6.8–7.99)	7.34 (7.26–7.42)	6.74	1.18	0
Lenvatinib	656	13.90 (12.86–15.02)	13.76 (13.68–13.83)	12.63	2.09	0
In total	1709	7.67 (7.31–8.06)	7.63 (7.58–7.68)	6.96	1.19	0

Table 5 ROR, PRR, EBGM, and BCPNN of TD AEs Under the Three Non-Selective RET MKIs Treatment

Drug	PT	N	ROR (95% CI)	PRR (95% CI)	EBGM05	BCPNN (IC025)	P
Sunitinib	HYPOTHYROIDISM	341	8.76 (7.87–9.75)	8.73 (8.62–8.83)	7.84	1.43	0
	MYXOEDEMA	7	25.19 (11.76–53.97)	25.19 (24.43–25.95)	12.62	2.89	0
	PRIMARY HYPOTHYROIDISM	4	15.01 (5.54–40.67)	15.01 (14.01–16.01)	6.32	2.18	0
	THYROID ATROPHY	4	50.18 (17.83–141.19)	50.18 (49.14–51.21)	18.99	3.77	0
	CENTRAL HYPOTHYROIDISM	3	5.6 (1.79–17.5)	5.6 (4.47–6.74)	2.14	0.8	0.01
Cabozantinib	HYPERTHYROIDISM	112	4.75 (3.94–5.72)	4.74 (4.56–4.93)	4.01	0.56	3.59E-72
	HYPOTHYROIDISM	485	10.13 (9.26–11.09)	10.09 (10–10.18)	9.12	1.63	0
Lenvatinib	HYPERTHYROIDISM	97	7.11 (5.82–8.69)	7.1 (6.9–7.3)	5.95	1.15	4.8E-110
	HYPOTHYROIDISM	544	19.84 (18.21–21.62)	19.67 (19.59–19.76)	17.77	2.59	0
	PRIMARY HYPOTHYROIDISM	4	20.96 (7.74–56.78)	20.96 (19.96–21.96)	8.82	2.66	9.57E-14
	THYROTOXIC CRISIS	7	6.97 (3.31–14.68)	6.97 (6.22–7.71)	3.7	1.12	5.03E-08

Subgroup Analysis

To investigate the association between the three non-selective RET MKIs and TD AEs, stratified analyses were performed based on age (≤65 and >65 years), gender (female and male), and weight (≤80 kg and >80 kg). In all subgroups, the signal values calculated by all the four algorithms were statistically significant, indicating a robust statistical correlation between the three non-selective RET MKIs and TD AEs (Table 6). In patients over 65 years receiving Cabozantinib and Lenvatinib, signal values were higher than that in patients aged ≤65 years old, suggesting a higher susceptibility to thyroid dysfunction adverse events among older patients. For Sunitinib, the signal values in patients aged ≤65 years old were higher than in patients aged over 65 years, indicating differential susceptibility based on age following Sunitinib treatment. In patients receiving Sunitinib or Lenvatinib, compared with males, signal values in females were higher, suggesting a higher likelihood of thyroid dysfunction adverse events in females after Sunitinib and Lenvatinib treatment. In female patients treated with Cabozantinib, the signal values were lower than in males, indicating a greater propensity for developing thyroid dysfunction adverse events in males post-Cabozantinib treatment. Regarding weight, signal values in patients weighted ≤80kg receiving Cabozantinib or Lenvatinib were higher than in patients weighted >80kg, pointing towards a higher prevalence of thyroid dysfunction adverse events in individuals weighing ≤80kg following Cabozantinib or Lenvatinib treatments. In patients weighted >80kg treated with Sunitinib, the signal

Table 6 Subgroup Analyses of Sunitinib-, Cabozantinib-, and Lenvatinib-Related Thyroid Dysfunction Adverse Events

Drug	Subgroup		Number	ROR (95% CI)	PRR (95% CI)	EBGM05	IC025	P
Sunitinib	Age	<=65	212	6.79 (5.94–7.76)	6.76 (6.63–6.89)	5.96	1.07	7.5E-232
		>65	126	3.58 (3.01–4.26)	3.57 (3.4–3.75)	3.05	0.15	3.04E-53
	Gender	Male	207	5.68 (4.96–6.51)	5.66 (5.53–5.8)	4.96	0.81	1.7E-176
		Female	153	6.25 (5.35–7.31)	6.22 (6.07–6.38)	5.42	0.96	3.2E-152
	Weight	<=80	81	4.1 (3.3–5.08)	4.08 (3.87–4.3)	3.37	0.35	3.14E-43
		>80	52	4.84 (3.7–6.32)	4.83 (4.56–5.09)	3.79	0.58	1.45E-36
Cabozantinib	Age	<=65	169	7.49 (6.46–8.68)	7.44 (7.3–7.59)	6.5	1.21	4.8E-215
		>65	194	8.09 (7.03–9.32)	8.04 (7.9–8.18)	6.97	1.3	2.9E-261
	Gender	Male	362	7.59 (6.84–8.42)	7.56 (7.45–7.66)	6.69	1.2	0
		Female	146	5.62 (4.79–6.6)	5.6 (5.44–5.76)	4.86	0.81	3.6E-124
	Weight	<=80	91	9.29 (7.58–11.39)	9.21 (9.01–9.42)	7.66	1.52	2.5E-149
		>80	28	7.03 (4.98–9.91)	6.99 (6.65–7.34)	5.18	1.12	5.21E-37
Lenvatinib	Age	<=65	194	10.29 (8.93–11.86)	10.21 (10.07–10.35)	8.95	1.67	0
		>65	263	10.95 (9.7–12.37)	10.85 (10.73–10.97)	9.47	1.72	0
	Gender	Male	222	11.3 (9.89–12.9)	11.21 (11.08–11.34)	9.81	1.79	0
		Female	404	15.69 (14.23–17.3)	15.5 (15.4–15.59)	13.96	2.26	0
	Weight	<=80	180	9.98 (8.6–11.57)	9.89 (9.74–10.04)	8.5	1.6	4.1E-307
		>80	30	5.34 (3.72–7.65)	5.32 (4.96–5.68)	3.89	0.73	1.72E-23

values were higher than in patients weighted ≤80kg, suggesting increased susceptibility to thyroid dysfunction adverse events among those weighed >80kg after Sunitinib treatment.

Analysis of Factors Independently Influencing TD AEs

Multivariate logistic regression analyses were conducted to assess factors independently influencing the occurrence of thyroid dysfunction adverse events (Figure 4). In patients receiving Sunitinib, age ≤65 years old was found to be a risk factor independently influencing the occurrence of TD AEs (OR=2.40 [1.66–3.50], p<0.001). In patients receiving Cabozantinib, weigh ≤80kg was identified as a risk factor (OR=1.89 [1.21–3.06], p=0.007). In patients receiving Lenvatinib, female (OR=1.45 [1.08–1.94], p=0.014) and weight >80kg (OR=1.69 [1.14–2.60], p=0.012) were indicated to be risk factors of the occurrence of TD AEs.

Time to Onset Analysis and Weibull Shape Parameter (WSP) Test

The time of onset for thyroid dysfunction adverse events (TD AEs) is illustrated in Figure 5, indicating that the majority of TD AEs manifested within the initial 30 days following treatment with the three non-selective RET MKIs. Following the Weibull Shape Parameter (WSP) test, the analysis revealed that patients treated with Sunitinib, Cabozantinib, or Lenvatinib exhibited upper limits of the 95% confidence interval for the shape parameter β below 1, indicative of an early failure type pattern for TD AEs. These findings imply a gradual reduction in the risk of TD AEs over time (Table 7).

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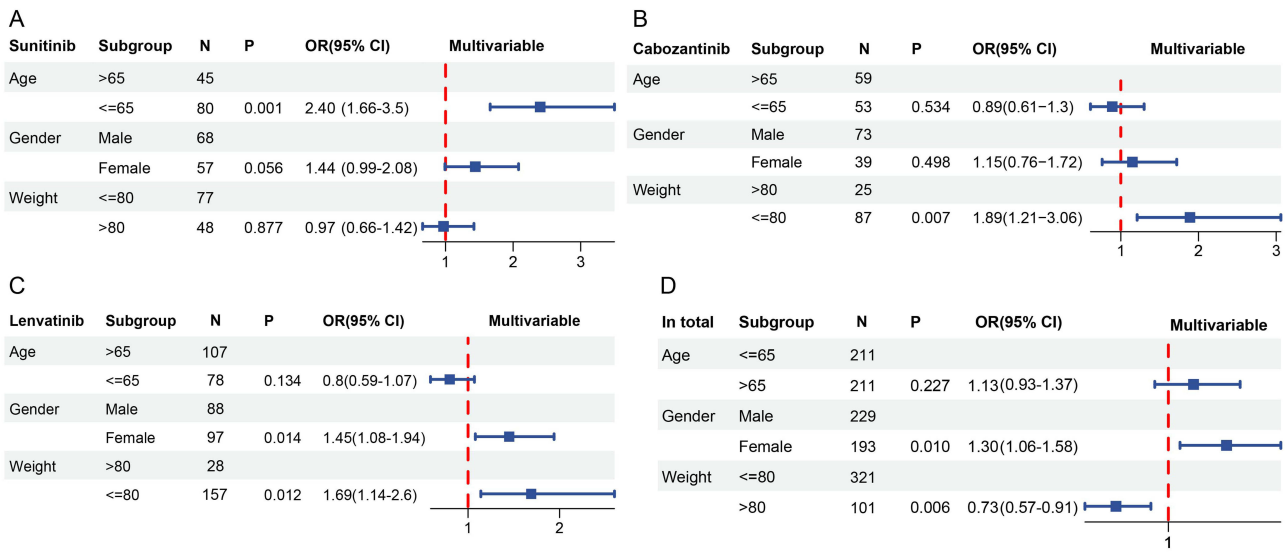

Figure 4 Results of multivariate logistic regression analyses of factors influencing TD AEs associated with the treatment of Sunitinib (**A**), Cabozantinib (**B**), Lenvatinib (**C**), and in total (**D**).

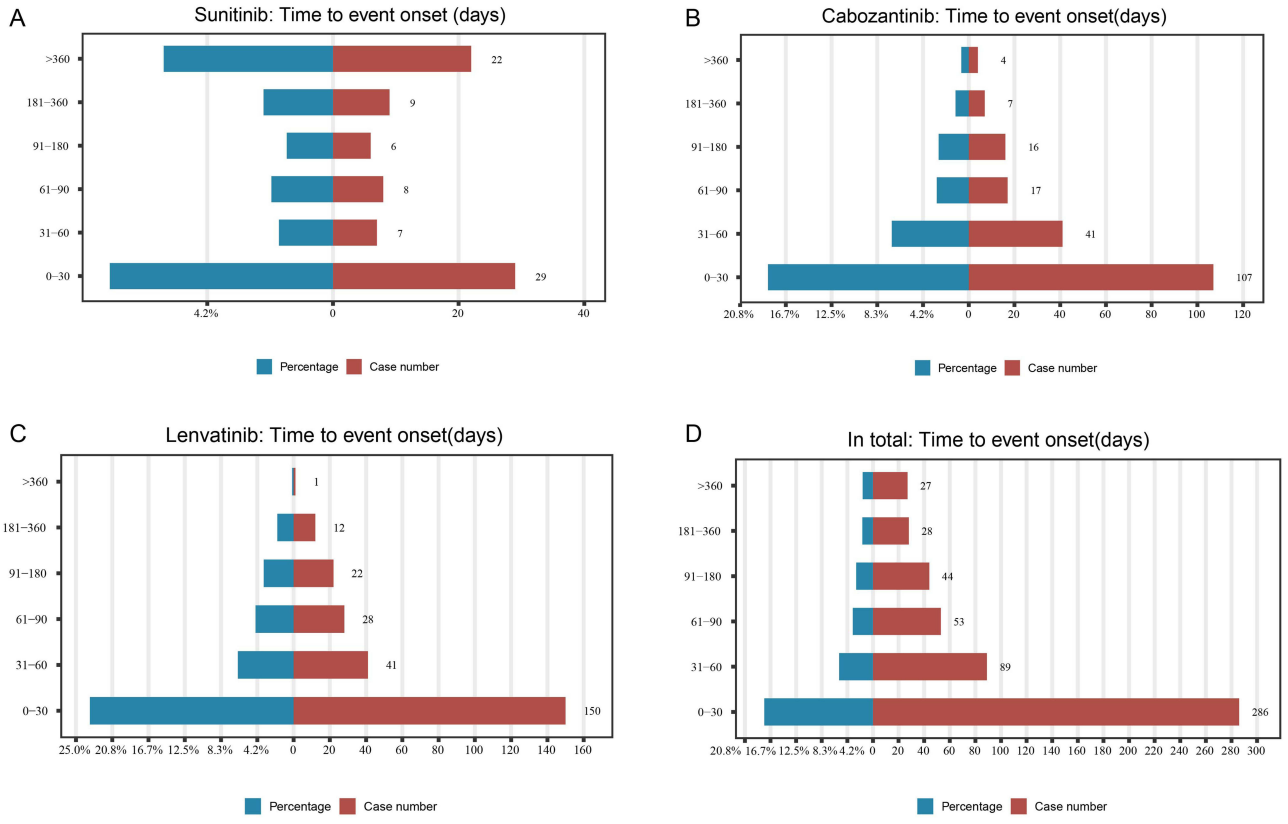

Figure 5 Results of time-to-event onset analyses of TD AEs associated with the treatment of Sunitinib (**A**), Cabozantinib (**B**), Lenvatinib (**C**), and in total (**D**).

Sensitivity Analysis

Indications may affect the signal values of Sunitinib, Cabozantinib, and Lenvatinib-related TD AEs. We excluded diseases (thyroid cancer, medullary thyroid cancer, thyroid cancer metastatic, anaplastic thyroid cancer, papillary thyroid

Table 7 The Results of Weibull Shape Parameter (WSP) Test

	Sunitinib	Cabozantinib	Lenvatinib	In total
Scale parameter: α (95% CI)	195.76 (119.46–272.07)	49.82 (41.41–58.22)	40.63 (34.12–47.14)	59.75 (51.59–67.91)
Shape parameter: β (95% CI)	0.59 (0.49–0.69)	0.89 (0.80–0.98)	0.81 (0.74–0.89)	0.66 (0.62–0.70)
Type	Early failure	Early failure	Early failure	Early failure

cancer, and follicular thyroid cancer) as TD AEs may occur preferentially in patients with these conditions. We also chose the role code as "primary suspect drug". After adjusting these factors, we recalculated the signal values (Table 8). The results showed that the signal values of Sunitinib-, Cabozantinib-, or Lenvatinib-related TD AEs were still statistically significant.

Causality Assessment

Globally, on the basis of signal values calculated by all the four algorithms, sensitivity analysis, TTO and WSP analyses, and evidence from existing studies, the majority of the criteria have been fulfilled, thus supporting a potential causal association (Table 9).

Discussion

At present, most of the articles related to non-selective RET kinase inhibitors and thyroid dysfunction are case reports and clinical trials. Due to the small sample size and other shortcomings, the relationship between the two is still unclear. The FAERS database records a large amount of real-world data, which helps to better reveal the relationship between them. In this study, we innovatively used four data mining methods, subgroup analyses, TTO analyses, and WSP tests to provide insight into the occurrence of TD AEs and non-selective RET MKIs, and investigate the clinical characteristics of patients with such AEs. To our knowledge, this is the first pharmacovigilance study to systematically explore the association between non-selective RET MKIs and TD AEs using real-world data.

Four data mining methods, including ROR, PRR, BCPNN, and EBGM were used to improve the reliability of this study. We found that Lenvatinib, Cabozantinib, and Sunitinib were significantly associated with TD AEs. Consistent with the drug label, Sorafenib and Vandetanib were not significantly associated with TD AEs, indicating that the results of our study had high reliability and robustness.

Our study reveals a significant association between the use of Cabozantinib and thyroid dysfunction signals compared to the other four non-selective RET kinase inhibitors. Specifically, Cabozantinib is significantly associated with both hypothyroidism and hyperthyroidism, and the correlation with the former is stronger. In the study of hypothyroidism caused by Cabozantinib, various mechanisms have been proposed: VEGF/R-TKIs may act as non-competitive inhibitors by blocking thyroid peroxidase to inhibit thyroid hormone biosynthesis and enhance type 3 deiodination, and the transport of iodothyronine is destroyed by inhibiting the transmembrane transport of thyroid-derived hormones, and inhibition of VEGF signaling leads to a decrease in the number of thyroid capillary fenestrations, which induces thyroid capillary degeneration and gradual depletion of thyroid function reserves. In the study of thyroid dysfunction caused by Cabozantinib, hypothyroidism is the most common, but there are also records of hyperthyroidism. This may be due to the destructive thyroiditis caused by Cabozantinib, which in turn causes transient thyrotoxicosis.

Table 8 The Signal Intensity Calculated by Four Algorithms After Adjusting Indication Factors

Drug	Number	ROR (95% CI)	PRR (95% CI)	EBGM05	IC025	P
Sunitinib	341	111.8 (100.21–124.74)	102.71 (102.61–102.81)	92.62	5	0
Cabozantinib	601	250.12 (228.99–273.2)	208.89 (208.81–208.96)	190.13	6.01	0
Lenvatinib	626	346.83 (317.24–379.19)	272.28 (272.21–272.35)	247.43	6.39	0

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Table 9 Causality Assessment of Thyroid Dysfunction Adverse Events (TD AEs) With Sunitinib, Cabozantinib, and Lenvatinib Based on Bradford Hill Criteria

Criterium	Findings	Criterium fulfilled
Strength of the association	We employed the ROR, PRR, BCPNN, and EBGM to assess the strength of the association between TD AEs and Sunitinib, Cabozantinib, and Lenvatinib. Although the four algorithms are not direct measures of risk, their results indicated there were strong signals.	√
Biological plausibility and experimental support	Sunitinib, Cabozantinib, and Lenvatinib can impact the blood supply and angiogenesis of the thyroid gland, influence the growth, proliferation, and differentiation of thyroid cells, as well as the synthesis and secretion of thyroid hormone, and thus leading to TD.	√
Coherence	Case reports, clinical studies, and animal research all indicate that the use ofSunitinib, Cabozantinib, and Lenvatinib may induce TD, although there may be inconsistencies in risk among different studies regarding various medications	√
Consistency	Results of disproportionality approaches were consistent across sensitivity analyses	√
Specificity	We used PTs from the narrow-scope search "Thyroid dysfunction (SMQ)" to ascertain TD AEs, and thus making the included PTs were as complete and specific as possible. However, due to data limitations in the FAERS database, it is impossible to determine the specificity of the association between the target drug and the target AEs	?
Biological gradient	The available data does not establish a precise relationship between dosage or duration and adverse reactions. Despite missing data, TD do occur within the therapeutic dose range.	?
Temporal relationship	Notwithstanding variable quality of reports due to missing data, TD AEs appear to occur early after drug administration, thus suggesting the need for patients' monitoring.	√
Analogy	The pharmacodynamic profiles of Sunitinib, Cabozantinib, and Lenvatinib overlap with the mechanisms known to cause TD.	√

Notes: √Relevant criterium is fulfilled based on pharmacovigilance data. ? Uncertainty in fulfillment of relevant criterium.

To our knowledge, only hypothyroidism was listed in the drug instructions for Lenvatinib. Our study revealed that besides hypothyroidism, the use of Lenvatinib can also result in hyperthyroidism and even thyroid crisis. Several possible mechanisms have been proposed in response to this phenomenon: Lenvatinib, as a multi-target tyrosine kinase inhibitor, could induce thyroid dysfunction, including hyperthyroidism, by influencing the blood supply and angiogenesis of the thyroid gland. While Lenvatinib effectively delays tumor growth by inhibiting the action of vascular endothelial growth factor (VEGF), this action could also impact thyroid function, leading to abnormal thyroid stimulation and heightened synthesis and release of thyroid hormones, ultimately causing hyperthyroidism. Lenvatinib may trigger autoimmune thyroid disease or inflammation through its effects on the immune system, resulting in thyroid dysfunction, including the onset of hyperthyroidism. Moreover, Lenvatinib might influence the growth, proliferation, and differentiation of thyroid cells, as well as the pathways for thyroid hormone synthesis and secretion, ultimately leading to hyperthyroidism. Thyroid crises could potentially manifest in patients due to any of these mechanisms.

In our study, the clinical use of Sunitinib is closely related to hypothyroidism, which is consistent with the drug instructions. Several evidences and hypotheses have been proposed to explain Sunitinib-induced hypothyroidism. (1) Reduction of thyroid hormone synthesis by inhibition of thyroid peroxidase. Studies have shown that Sunitinib has antithyroid activity similar to that of antithyroid drugs, so it may cause hypothyroidism. (2) Induction of transient hypothyroidism by blockade of iodine uptake. In a study examining the effects of Sunitinib on thyroid function in patients with gastrointestinal mesenchymal tumors, significant changes in 123I uptake were found while taking the drug. This suggests that the underlying mechanism for its contribution to hypothyroidism is impaired iodine uptake, which may specifically be a direct effect of Sunitinib on the sodium iodide symporter (NIS) or the TSH receptor. (3) And induction of destructive thyroiditis by follicular cell apoptosis. In a number of studies examining the relationship between Sunitinib

treatment and TD AEs, patients were identified who first experienced thyroid-stimulating hormone (TSH) suppression followed by loss of thyroid tissue. This suggests that Sunitinib may induce destructive thyroiditis through follicular cell apoptosis, leading to hypothyroidism. However, the mechanism of this adverse event is unknown, and further studies are needed to confirm the mechanism of hypothyroidism induced by RET kinase inhibitors. In addition, it has been hypothesized that retinoic acid receptors may also be involved. It is known that the action of thyroid hormones depends on the heterodimerization of the nuclear thyroid hormone receptor with the retinoic acid receptor. Sunitinib may competitively affect the binding of thyroid hormone receptors to retinoic acid receptors, which in turn triggers thyroid hormone dysregulation.

We used subgroup analyses to explore in depth the effects of age, gender, and body weight on thyroid dysfunction induced by non-selective RET multi-kinase inhibitors. Subgroup analyses showed that the results of the study presented different profiles for the three drugs. In patients treated with Cabozantinib and Lenvatinib, older patients were more likely to experience adverse events of thyroid dysfunction compared to younger patients. In terms of age, the increased risk of adverse reactions in elderly patients may stem from the decline in their organ function, especially the weakened metabolism and excretion capacity of the liver and kidneys, which may lead to the accumulation of drugs in the body, thereby elevating the chance of adverse reactions. In addition, elderly patients are often accompanied by multiple chronic diseases and need to take multiple medications, which may trigger drug–drug interactions and further aggravate the risk of adverse reactions. Therefore, when prescribing to patients aged >65 years, clinicians should fully consider the possible risks associated with the age factor of the patients to ensure the safety and efficacy of the treatment. However, multivariate logistic regression results did not show that ages >65 years were an independent risk factor for thyroid dysfunction in patients receiving Cabozantinib or Lenvatinib. This may be due to a small sample size, and conclusions about factors affecting TD need to be further validated by larger studies or clinical trials. In contrast, results of subgroup analyses showed that patients aged ≤65 years and receiving Sunitinib were more likely to develop TD AEs. Multivariate logistic regression analysis also showed that age ≤65 years was an independent risk factor for TD in patients treated with Sunitinib. The underlying mechanism remains unclear. One possible explanation is that estrogen could reduce the expression of ABCB1 and ABCG2, the efflux transporter genes of sunitinib, leading to increased drug concentration in younger patients (higher estrogen) and decreased drug concentration in older patients (lower estrogen).[39] Regarding gender, the results of subgroup analyses were consistent with a previous retrospective study published in Japan by Akaza et al. However, in patients treated with Cabozantinib, the probability of TD in men is higher than that in women. Studies have shown that CYP3A4 is a key enzyme in Cabozantinib metabolism. Parkinson et al found that the activity of CYP3A4 in women is twice as high as that in men, which may lead to a lower clearance rate of Cabozantinib in men, resulting in higher systemic exposure, which leads to a higher probability of TD in men. The results of regression analysis showed that female was a risk factor for the occurrence of TD AEs in the patients receiving Lenvatinib, which was consistent with the results of subgroup analyses. However, gender was not identified as an independent risk factor in patients receiving Cabozantinib or Sunitinib. This may be due to the smaller sample size included in the multivariate logistic regression compared to the subgroup analyses. As for body weight, both the results of regression analyses and subgroup analyses showed that patients weighing ≤80kg who received Cabozantinib or Lenvatinib were more likely to have TD AEs. The number of relevant previous studies was small, we speculated that this phenomenon was related to changes in estrogen and pharmacokinetics. The conclusions and mechanisms need to be further verified by larger studies or clinical trials.

The use of time-to-onset (TTO) analysis provides insights into the temporal dynamics of thyroid dysfunction adverse events associated with non-selective RET multi-kinase inhibitors. The results of TTO analyses and WSP tests conducted in our study showed that most patients develop TD AEs within 0–30 days of treatment with RET MKIs and all TD AEs have an early failure phenotype. This finding has important implications for patient management and treatment strategies. It suggests that doctors should be extra vigilant for the development of TD AEs in the early stages after patients are started on these medications and take more active monitoring and management measures. At the same time, the risk of TD AEs gradually decreases over time, which opens up the possibility of long-term medication use. Therefore, during clinical use of the drug, doctors need to continuously monitor the patient's thyroid function and adjust the treatment plan according to the patient's specific situation.

The Bethesda System for Reporting Thyroid Cytopathology is a widely used framework for evaluating thyroid nodules. Category II (benign) nodules generally exhibit a low risk of malignancy (0–3%), while Category III–IV (atypia of undetermined significance or follicular lesion of undetermined significance) nodules show a slightly higher malignancy risk (15–40%).[43,44] The surgical management and the possible complications are also needed to be considered[45] The combination of this system and the choice of surgical management can help clinicians better treat patients with thyroid nodules after non-selective RET MKIs treatment.

Conclusion

In conclusion, in this pharmacovigilance study, we identified a potential correlation between RET kinase inhibitors and TD AEs based on the FAERS database. The results of TTO and WSP analysis suggested that doctors should be extra vigilant for the development of TD AEs in the early stages after patients. This finding provides clinicians with a new understanding of medication risk and contributes to safer and more effective patient care. At the same time, there are some limitations to this study. First, FAERS database is a self-reporting system with some inherent selection bias; therefore, we could not calculate the incidence of TD AEs associated with non-selective RET MKIs or establish a causality between TD AEs and non-selective RET MKIs; second, due to the lack of dietary data in the FAERS database, we could not evaluate the impact of dietary factors such as iodine intake on the occurrence of TD AEs. Further clinical studies are needed to confirm the relevant findings of this study. With the widespread use of RET kinase inhibitors, combining FAERS data with other data sources is crucial for monitoring RET kinase inhibitor-induced TD AEs. In addition, further studies are needed to elucidate the mechanisms involved in the induction of TD AEs by RET kinase inhibitors.

Abbreviations

FAERS, Food and Drug Administration Adverse Event Reporting System; TTO, Time-to-onset; WSP, Weibull Shape Parameter; RTKs, Receptor tyrosine kinases.

MKIs, Multikinase inhibitors; AEs, Adverse events; TD, Thyroid dysfunction; HF, Heart failure; TSH, Thyroid stimulating hormone; FDA, Food and Drug Administration's; PS, Primary suspected; MedDRA, Medical Dictionary for Regulatory Activities; ADR, Adverse drug reaction; PTs, Preferred Terms; SMQs, Standardized MedDRA Queries; ROR, Reported odds ratio; PRR, Proportional reported odds ratio; BCPNN, Bayesian confidence propagation neural network; EBGM, Gamma Poisson reduction method; VEGF, Vascular endothelial growth factor; Sodium iodide symporter, (NIS).

Data Sharing Statement

The data used in this study were extracted from online repositories: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-systemfaers/fda-adverse-event-reporting-system-faers-public-dashboard.

Ethics Approval and Consent to Participate

This current study involved the analysis of anonymised data from the publicly available FAERS database. In accordance with Article 32 of China's "Notice on the Issuance of Measures for the Ethical Review of Human Life Science and Medical Research" (2023), which allows for the waiver of ethical review for research using public, anonymised information data that does not harm human beings or involve sensitive personal information or commercial interests, this study was determined to be exempt from institutional ethics approval. The Ethics Committee of Changzhi People's Hospital reviewed the protocol and data handling processes of this research and confirmed that this study complied with the above regulations and was exempt from ethical review.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no potential financial and non-financial competing interests in this work.

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