

Endocrine toxicity associated with anti - neoplastic drugs: a pharmacovigilance analysis based on the FDA adverse event reporting system database

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Abstract

Background

Anti - neoplastic drugs are effective for malignant tumors, but they frequently cause severe adverse drug reactions (ADRs), which seriously affect treatment continuity and patient prognosis. Post - marketing real - world safety monitoring is therefore critical.

Methods

We conducted a retrospective pharmacovigilance study based on the FDA Adverse Event Reporting System (FAERS). Reports from 2004 Q1 to 2025 Q4 were included. Disproportionate analysis was used to detect safety signals. LASSO and multivariable logistic regression were applied to identify independent influencing factors. Finally, we analyzed the time to onset (TTO) of endocrine toxicity.

Results

A total of 40,416 qualified reports involving 300 anti - neoplastic drugs were enrolled. The incidence was higher among female patients (51.05%) than among male patients (38.55%), with a median age of 57 years. 37.04% of the reported patients were aged between 18 and 64.9 years. 5,557 patients (13.75%) experienced fatal or life - threatening outcomes. The top three drugs with the highest number of reported events were pembrolizumab (reporting odds ratio (ROR) = 13.57), nivolumab (ROR = 10.79) and ipilimumab (ROR = 20.68). 44.54% of events occurred within the first month; there were significant differences in median TTO between males and females, or between the fatal and non - fatal groups. Furthermore, analysis using the Weibull shape parameter (WSP) indicated that 17 of the top 30 drugs followed an early failure model.

Conclusions

This study identified a robust safety signal between anti - neoplastic drug and endocrine toxicity. Clinicians should strengthen regular monitoring for this adverse event during clinical medication to reduce treatment - related complications. Given the inherent limitations of the FAERS database, future pharmacoeconomic studies incorporating comprehensive causal relationship assessments are still required for further validation.

1 Introduction

Although anti - neoplastic therapies have markedly prolonged patient survival, they are frequently accompanied by a range of adverse effects, among which endocrine toxicity has emerged as a growing clinical concern in contemporary oncology. The advent of novel targeted agents and immunotherapies - notably immune checkpoint inhibitors and tyrosine kinase inhibitors - has shifted endocrine side effects from a minor issue associated with conventional chemotherapy to a critical factor that compromises quality of life, treatment compliance, and even overall prognosis [1]. The endocrine disturbances induced by these drugs involve multiple glands, manifesting primarily as hypophysitis, hypothyroidism, adrenal insufficiency, and hypogonadism. Their underlying pathophysiology is thought to stem from two major mechanisms: autoimmune - mediated glandular damage and direct cytotoxic actions of the agents [2]. The advent of immune checkpoint inhibitors (ICIs) has transformed the therapeutic landscape for diverse malignancies, yet their efficacy is often tempered by immune - related adverse events (irAEs). Endocrine toxicities constitute a clinically significant subset of these complications, with the thyroid, pituitary, and adrenal glands being the most frequently involved organs [3]. Among

endocrine irAEs, thyroid dysfunction occurs most commonly during ICI therapy and exhibits a substantially higher incidence than toxicities affecting other endocrine glands [4]. Notably, anti - PD-1/PD - L1 antibodies confer a higher risk of thyroid dysfunction than anti - cytotoxic T - lymphocyte - associated protein 4 (CTLA - 4) antibodies; this complication is often irreversible and mandates sustained thyroid hormone replacement. In contrast, hypophysitis represents a severe endocrine toxicity that occurs predominantly with anti - CTLA - 4 therapy, with reported incidence rates of approximately 10% - 15% [5]. In addition to ICIs, tyrosine kinase inhibitors (TKIs) elicit a characteristic spectrum of endocrine adverse effects. By targeting specific kinases to disrupt oncogenic signaling, TKIs may inadvertently impair the function of normal endocrine tissues [6]. Multi - targeted agents such as sunitinib and sorafenib, for example, are frequently associated with hypothyroidism, a complication thought to arise from inhibited thyroid angiogenesis or direct follicular cell cytotoxicity [7].

The identification, grading and clinical management of endocrine toxicity induced by anti - neoplastic interventions still face numerous unresolved challenges. Firstly, current assessment criteria are constrained by inherent limitations: the universally utilized Common Terminology Criteria for Adverse Events (CTCAE) presents unsatisfactory reliability in the grading of endocrine toxicity, and the distinction between Grade 2 and Grade 3 toxic reactions is particularly ambiguous. Secondly, long - term follow - up management remains insufficient. As the survival duration of cancer patients continues to prolong, long - term endocrine adverse events associated with anti - neoplastic treatment have gradually manifested, which mandates the establishment of a standardized long - term follow - up system to address delayed endocrine toxicity [8]. Thirdly, the implementation of drug monitoring and therapeutic regimen optimization needs to be intensified. Considering that anti - neoplastic drugs may trigger severe endocrine toxicity, the conduction of therapeutic drug monitoring and population pharmacokinetic/pharmacodynamic (PK/PD) investigations exerts a pivotal role in optimizing dosing schedules, minimizing toxic hazards and maximizing clinical therapeutic effects [9]. Although studies have revealed differences in the spectrum of endocrine toxicity across various ICI treatment regimens, our understanding of the immunological mechanisms driving these differences remains limited. For cancer patients, treatment regimens often combine multiple drugs. While combination therapy correlates with a higher risk of endocrine complications, the wide diversity of combination regimens makes it difficult to attribute specific toxic effects to individual agents. The use of multiple combined drugs may produce synergistic or additive endocrine toxic effects, but current research has not sufficiently analyzed these complex scenarios [10]. Furthermore, the overall effectiveness of pharmacovigilance frameworks is inextricably linked to the accurate and timely characterization of adverse reaction - related clinical manifestations. Immune - mediated endocrine adverse reactions often manifest with heterogeneous, non - specific symptoms that show considerable overlap with paraneoplastic syndromes or metastatic sequelae attributable to the primary malignancy, resulting in significant delays in early clinical recognition [11]. Critically, the current lack of well - validated, reproducible predictive biomarkers imposes major constraints on precise, patient - specific risk stratification, eliminating the possibility of pre - treatment identification of individuals at elevated risk of developing severe endocrine - related toxicity. In turn, this gap has resulted in the widespread implementation of generalized, non - individualized monitoring strategies. This uniform monitoring paradigm not only contributes to unwarranted increases in healthcare system costs, but also introduces critical clinical risks, as it may fail to prioritize and closely surveil the subpopulation of patients at the highest risk of severe events [5].

As one of the world's largest spontaneous adverse event reporting systems, the FAERS database serves as the cornerstone of real - world drug safety data. It captures rare, delayed, or population - specific adverse events that are difficult to detect in clinical trials due to limited sample sizes, short follow - up periods, or highly selected patient populations, underscoring FAERS' unique value in identifying unknown or unexpected safety signals [12, 13]. In pharmacovigilance, the FAERS serves as a fundamental resource for both signal detection and quantitative assessment. By mining this large - scale real - world database and calculating disproportionality measures - such as the ROR - researchers can identify adverse events whose observed frequencies significantly exceed background expectations, thereby effectively prioritizing potential safety signals that warrant further investigation [14, 15]. Furthermore, FAERS - based analyses enable the construction of a comprehensive adverse event profile for a given drug, encompassing affected

System Organ Classes (SOCs), the most frequently reported Preferred Terms (PTs), patient demographic variables (e.g., age and sex distribution), and temporal trends in event occurrence. This multidimensional approach offers clinicians far more granular and actionable safety intelligence than is typically available in the product labeling [16, 17]. The FAERS serves as a critical infrastructure within pharmacovigilance, fulfilling essential functions in the detection of novel safety signals, quantification of drug - event associations, and delineation of comprehensive safety profiles [18]. Its methodological advantages derive from real - world data generation, large - scale case accumulation, and a standardized framework for disproportionality analysis. As an open - access repository, FAERS has been extensively utilized in post - marketing surveillance of adverse drug reactions. In light of the substantial clinical benefits that anti - neoplastic therapeutics confer upon patients, a systematic evaluation of the relationship between these agents and endocrine toxicities - and the determinants modulating this relationship - is warranted.

Accordingly, this retrospective study employed disproportionality analysis and regression models to investigate the safety signals of anti - neoplastic drugs using FAERS data. We further assessed the influencing factors of the associated adverse reactions and performed subgroup stratification. Our findings aim to provide real - world evidence to support rational medication use and safety management of anti - neoplastic drugs in clinical oncology.

2 Methods

2.1 Data sources

In the present research, we retrieved and analyzed adverse - event datasets of anti - neoplastic agents sourced from the FAERS, with the observational timeframe spanning Q1 2004 to Q4 2025. Raw datasets downloaded from the FAERS repository are stored in American Standard Code for Information Interchange (ASCII) - formatted files, which are separated into seven data modules, including patient baseline demographics and administrative profiles (DEMO), medication - related information (DRUG), reporter source logs (RPRS), coded adverse - event descriptions (REAC), therapeutic medication records (THER), clinical outcome information (OUTC), as well as treatment - indication entries (INDI).

2.2 Data processing

In accordance with the US Food and Drug Administration guidelines on eliminating duplicate data, duplicate reports were excluded; for cases with the same medical record number, the most recent version was retained. Links between records were established using primary identifiers. Primary suspect drugs (PS drugs) were identified by searching for the Preferred Term (PT) 'endocrine toxicity', standardized according to the Medical Dictionary for Regulatory Activities (MedDRA). Drug names were further standardized using the Anatomical Therapeutic Chemical (ATC) classification system (https://atcddd.fhi.no/atc_ddd_index/). **Figure 1** illustrates the workflow for extracting and cleaning adverse events related to endocrine toxicity and anti - neoplastic drugs.

2.3 Regression analysis

Univariate screening of suspected drugs was conducted using three predefined criteria: a lower bound of the 95% confidence interval (CI) for the ROR greater than 1, a cumulative event count exceeding 300, and an adjusted p - value below 0.01. Agents achieving statistical significance ($p < 0.01$) in this univariate analysis were subsequently subjected to least absolute shrinkage and selection operator (LASSO) regression. To identify independent risk factors for endocrine toxicity related to anti - neoplastic drugs, a multivariate logistic regression model was then constructed, incorporating both the drug variables selected by LASSO and the baseline patient characteristics as covariates.

2.4 Time to onset analysis

TTO was defined as the temporal interval between the date of drug administration initiation (START_DT in the THER file) and the documented date of the adverse event (EVENT_DT in the DEMO file). Cases with incomplete, invalid, or incorrectly

recorded dates were omitted from the analytical dataset. Descriptive statistics for TTO comprised the median, first quartile (IQR), and WSP. The Weibull model incorporates a scale parameter (α) and a shape parameter (β), the latter of which governs the temporal pattern of event risk. According to the magnitude of β and the bounds of its 95% CI, adverse drug events (ADEs) were categorized into three mechanistic profiles: an early failure pattern, denoting a declining risk over time ($\beta < 1$, 95% CI < 1); a random failure pattern, signifying a time - invariant risk ($\beta \approx 1$, 95% CI inclusive of 1); and a wear - out failure pattern, representing an escalating risk over time ($\beta > 1$, 95% CI > 1).

2.5 Statistical analysis

Four pharmacovigilance algorithms were employed to analyze adverse reaction signals: the ROR, the Proportional Reporting Ratio (PRR), the Bayesian Confidence Propagation Neural Network (BCPNN), and the Multinomial Gamma - Poisson Shrinker (MGPS). The ROR method served as the primary statistical measure, with a higher value indicating a stronger association between the anti - neoplastic drug and the risk of endocrine toxicity. The detailed calculation formulas for these methods are shown in **Tables 1 and 2**.

Table 1 Two -by - two contingency table for disproportionality analyses.

Type of drug	N of target adverse events	N of other adverse events	Total
Target drug	a	b	a+b
All other drugs	c	d	c+d
Total	a+c	b+d	a+b+c+d

Table 2 Overview of the main algorithms used for signal detection.

Algorithm	Publicity	Standard for generating signals
ROR	$ROR = \frac{a/b}{c/d}$	Lower 95% CI > 1 , $N \geq 3$
PRR	$PRR = \frac{a/(a+b)}{c/(c+d)}$	$PRR \geq 2$, $N \geq 3$
MGPS	$EBGM = \frac{a(a+b+c+d)}{(a+b)(a+c)}$	Lower 95% CI > 2
BCPNN	$IC = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$	Lower 95% CI > 0 , $N > 0$

3 Results

3.1 Descriptive analysis

Data mining analysis identified a positive correlation between 300 anti - neoplastic agents and endocrine toxicity, which was corroborated by 40, 416 individual case reports (**Table 3**). Geographical distribution analysis revealed that the majority of anti - neoplastic drug - associated endocrine toxicity adverse events were reported from the United States (12, 753; 31.55%) and Japan (9, 324; 23.07%). After excluding 10, 636 patients with missing age information (accounting for 26.32% of total cases), the median age of included patients was 57 years (IQR: 34 - 73), with the largest proportion of cases (14, 970; 37.04%) concentrated in the 18 - 64.9 years age group. Body weight of affected patients was predominantly distributed in the range of 50 - 100 kg (n = 9, 515; 23.54%). Following exclusion of 4, 201 cases with unrecorded gender data (10.39%), female patients (n = 20, 633; 51.05%) accounted for a significantly higher proportion than male patients (n = 15, 582; 38.55%). The primary reporters of these adverse reactions were physicians (n = 18, 522; 45.83%) and consumers (n = 8, 951; 22.15%). Notably, 5, 557 patients (13.75%) developed fatal or life - threatening clinical outcomes. As illustrated in **Figure 2**, the annual number of reported cases of anti - neoplastic drug - related endocrine toxicity has exhibited an overall upward trend since 2004, reaching a peak of 5, 080 cases (12.57% of the total 22 - year cohort) in 2024.

Table 3 Clinical characteristics of reports with endocrine toxicity.

Characteristics	Case number (n)	Case proportion (%)
Gender		
Female	20, 633	51.05%
Male	15, 582	38.55%
missing	4, 201	10.39%
Weight		
≤50 kg	1, 454	3.60%
≤100 kg	914	2.26%
50–100 kg	9, 515	23.54%
missing	28, 533	70.60%
Age		
<18	2, 237	5.53%
>85	416	1.03%
18–64.9	14, 970	37.04%
65–85	12, 157	30.08%
missing	10, 636	26.32%
OCCP_COD		
Medical Doctor	18, 522	45.83%
Health professional	5, 368	13.28%
Consumer	8, 951	22.15%
Other	4, 213	10.42%
Pharmacist	2, 057	5.09%
missing	1, 204	2.98%
Reporting country		
United States	12, 753	31.55%
Japan	9, 324	23.07%
France	2, 380	5.88%
Germany	2, 084	5.15%
Canada	2, 077	5.14%
United Kingdom	1, 269	3.14%
Outcomes		
Congenital Anomaly	14	0.03%
Death	3, 526	8.72%
Disability	421	1.04%

Hospitalization	13, 355	33.04%
Life-Threatening	2, 031	5.03%
Required Intervention	55	0.14%
Other	17, 785	44.00%
missing	3, 229	7.99%

3.2 Disproportionality analysis

After data cleaning and analysis, a total of 300 anti - neoplastic drugs with positive endocrine toxicity signals were identified. The top 30 anti - neoplastic agents, ranked by the number of reports, are listed in **Table 4**. The top five drugs are: pembrolizumab (ROR = 13.57; 95% CI: 13.16 - 14.00), nivolumab (ROR = 10.79; 95% CI: 10.46 - 11.13), ipilimumab (ROR = 20.68; 95% CI: 19.77 - 21.63), lenvatinib (ROR = 10.33; 95% CI: 9.81 - 10.88), and β - interferon A (ROR = 1.45; 95% CI: 1.38 - 1.52). A subsequent subgroup analysis of all anti - neoplastic drugs revealed that immune checkpoint inhibitors accounted for the highest number of endocrine toxicity cases and had the highest ROR value; molecularly targeted therapies had the second - highest number of cases, while aromatase inhibitors ranked second in terms of ROR value (**Figure 3**). Furthermore, among these 300 anti - neoplastic drugs, the prescribing information for 272 included warnings regarding the risk of endocrine toxicity, while the prescribing information for the remaining 28 did not include such warnings (e.g., docetaxel, gemcitabine, ifosfamide, etc.).

Table 4 The top 30 anti - neoplastic agents associated with ADE of endocrine toxicity.

Ranking	Drug	Cases	ROR (95% CI)	PRR (χ^2)	EBGM (EBGM05)	IC (IC025)
1	Pembrolizumab	4548	13.57 (13.16-14.00)	12.54 (46963.57)	12.15 (11.78)	3.60 (3.55)
2	Nivolumab	4395	10.79 (10.46-11.13)	10.14 (35244.99)	9.84 (9.54)	3.30 (3.25)
3	Ipilimumab	2208	20.68 (19.77-21.63)	18.29 (35730.65)	18.00 (17.21)	4.17 (4.09)
4	Lenvatinib	1548	10.33 (9.81-10.88)	9.72 (12055.89)	9.62 (9.14)	3.27 (3.18)
5	Interferon Beta 1A	1522	1.45 (1.38-1.52)	1.44 (205.56)	1.44 (1.37)	0.52 (0.45)
6	Atezolizumab	1391	9.27 (8.78-9.79)	8.79 (9562.96)	8.71 (8.24)	3.12 (3.03)
7	Carboplatin	1332	4.28 (4.05-4.52)	4.19 (3224.40)	4.16 (3.94)	2.06 (1.97)
8	Cabozantinib	1281	5.02 (4.75-5.31)	4.89 (3951.04)	4.85 (4.59)	2.28 (2.19)
9	Sunitinib	1094	4.49 (4.23-4.77)	4.39 (2859.72)	4.36 (4.11)	2.13 (2.03)
10	Methotrexate	1013	1.10 (1.04-1.17)	1.10 (9.68)	1.10 (1.04)	0.14 (0.05)
11	Denosumab	917	0.86 (0.81-0.92)	0.86 (20.62)	0.86 (0.81)	-0.21 (-0.31)
12	Alemtuzumab	851	11.92 (11.11-12.78)	11.10 (7826.04)	11.04 (10.29)	3.46 (3.34)
13	Lenalidomide	817	0.33 (0.31-0.35)	0.33 (1122.39)	0.33 (0.31)	-1.59 (-1.69)
14	Rituximab	797	1.08 (1.00-1.15)	1.07 (4.17)	1.07 (1.00)	0.10 (0.00)
15	Octreotide	745	4.49 (4.17-4.83)	4.39 (1948.98)	4.37 (4.06)	2.13 (2.01)
16	Bevacizumab	716	1.47 (1.36-1.58)	1.46 (104.34)	1.46 (1.35)	0.54 (0.44)
17	Zoledronic Acid	660	1.61 (1.49-1.74)	1.60 (149.79)	1.60 (1.48)	0.68 (0.56)
18	Durvalumab	567	6.28 (5.77-6.83)	6.06 (2403.31)	6.04 (5.55)	2.59 (2.46)
19	Leuprorelin	430	0.81 (0.74-0.89)	0.81 (18.22)	0.82 (0.74)	-0.29 (-0.43)
20	Peginterferon Alfa 2A	418	1.99 (1.80-2.19)	1.97 (201.17)	1.97 (1.79)	0.98 (0.83)
21	Axitinib	413	4.04 (3.66-4.46)	3.96 (917.40)	3.95 (3.58)	1.98 (1.83)
22	Imatinib	371	0.95 (0.86-1.05)	0.95 (0.93)	0.95 (0.86)	-0.07 (-0.22)
23	Paclitaxel	361	1.42 (1.28-1.58)	1.42 (45.11)	1.42 (1.28)	0.51 (0.35)
24	Pazopanib	348	2.14 (1.92-2.38)	2.12 (207.69)	2.12 (1.91)	1.08 (0.92)
25	Pemetrexed	323	3.61 (3.23-4.03)	3.55 (592.86)	3.54 (3.17)	1.82 (1.65)
26	Cyclophosphamide	316	1.49 (1.34-1.67)	1.49 (50.87)	1.49 (1.33)	0.57 (0.41)
27	Everolimus	275	1.08 (0.96-1.22)	1.08 (1.61)	1.08 (0.96)	0.11 (-0.06)
28	Ibrutinib	270	0.58 (0.52-0.66)	0.58 (79.96)	0.59 (0.52)	-0.77 (-0.95)
29	Doxorubicin	267	1.16 (1.03-1.31)	1.16 (6.06)	1.16 (1.03)	0.22 (0.04)
30	Nilotinib	252	1.44 (1.27-1.63)	1.43 (32.99)	1.43 (1.26)	0.52 (0.33)

3.3 Risk factors for endocrine toxicity related to anti - neoplastic agents

We began by performing univariate screening on all suspected drugs, retaining only those with a case count > 300, an ROR lower 95% CI > 1, and a corrected p - value < 0.01. The drugs achieving univariate significance (p < 0.01) were then subjected to LASSO regression, which selected 20 agents for further evaluation (**Figure 4**). In the next step, these 20 drugs, in combination with patient demographic and clinical data, were incorporated into a multivariate logistic regression model (**Figure 5**). This analysis ultimately revealed that 18 drugs - notably ipilimumab, alemtuzumab, pembrolizumab, atezolizumab, carboplatin, sunitinib, and cabozantinib - constituted independent risk factors for endocrine adverse events.

3.4 Time to onset analysis

To maximize data integrity, entries containing discrepant or absent temporal information were omitted, resulting in a reduced analytical sample relative to the source dataset. **Figure 6** depicts the temporal distribution of endocrine toxicities, with 44.54% of affected individuals (n = 6, 923) experiencing onset within the first month of therapy. The TTO and WSP results for the top 30 offending anti - neoplastic drugs are catalogued in **Table 5**. Application of Weibull distribution analysis revealed that 56.67% of these drugs conformed to an early failure profile, signifying a concentrated risk period shortly after treatment commencement followed by a gradual decline in hazard. Subgroup - specific Kaplan - Meier curves are displayed in **Figure 7**. Sex - stratified analysis demonstrated a median TTO of 52 days (IQR: 15 - 133) in men (n = 15, 582) versus 60 days (IQR: 14 - 210) in women (n = 20, 633), with a statistically significant disparity between sexes (P < 0.0001). Similarly, TTO exhibited significant heterogeneity by clinical outcome (P < 0.0001): fatal outcomes (n = 3, 526) were associated with a markedly earlier median onset at 35 days (IQR: 10 - 112.8), whereas non - fatal cases (n = 36, 890) occurred at a median of 59 days (IQR: 16 - 174).

Table 5 TTO for the top 30 anti - neoplastic associated with ADE of endocrine toxicity.

SN	Drug	Cases	TTO (days)		Weibull distribution				Failure type
					Scale parameter		Shape parameter		
		n	Median	IQR	α	95% CI	β	95% CI	
1	Pembrolizumab	1277	57.00	20.00-135.00	91.87	85.58-98.62	0.82	0.78-0.85	Random Failure
2	Nivolumab	1952	58.00	24.00-127.00	97.38	92.08-102.99	0.84	0.81-0.87	Random Failure
3	Ipilimumab	924	52.00	23.00-84.00	71.77	66.97-76.91	0.99	0.94-1.03	Random Failure
4	Lenvatinib	618	39.00	13.00-119.75	72.76	65.15-81.27	0.75	0.71-0.80	Random Failure
5	Interferon Beta 1A	598	861.50	288.00-2090.00	1357.74	1235.37-1492.23	0.89	0.84-0.95	Random Failure
6	Atezolizumab	562	72.00	21.00-147.00	109.42	98.47-121.60	0.83	0.78-0.88	Random Failure
7	Carboplatin	559	63.00	23.00-145.00	101.16	91.71-111.57	0.89	0.84-0.95	Random Failure
8	Cabozantinib	474	31.00	15.00-68.75	64.17	56.81-72.48	0.78	0.74-0.84	Random Failure
9	Sunitinib	328	64.00	16.00-275.75	152.16	127.64-181.39	0.65	0.60-0.71	Early Failure
10	Methotrexate	83	480.00	178.00-1584.00	797.42	567.87-1119.77	0.66	0.56-0.79	Early Failure
11	Denosumab	87	84.00	14.00-364.00	178.07	122.17-259.53	0.59	0.50-0.69	Early Failure
12	Alemtuzumab	232	366.50	130.25-742.50	465.37	387.27-559.23	0.73	0.66-0.81	Early Failure
13	Lenalidomide	187	112.00	28.50-365.00	223.30	177.68-280.63	0.66	0.59-0.74	Early Failure
14	Rituximab	93	94.00	14.00-301.00	187.33	132.92-264.02	0.63	0.54-0.73	Early Failure
15	Octreotide	162	455.00	73.00-1515.50	737.00	569.78-953.29	0.63	0.56-0.71	Early Failure
16	Bevacizumab	268	82.50	41.00-152.00	133.40	115.57-153.97	0.88	0.81-0.96	Random Failure
17	Zoledronic Acid	151	140.00	14.50-533.50	230.05	169.00-313.15	0.54	0.48-0.62	Early Failure
18	Durvalumab	203	46.00	20.00-106.50	77.99	65.91-92.27	0.87	0.78-0.96	Random Failure
19	Leuporelin	95	92.00	28.50-365.50	228.11	153.72-338.50	0.54	0.46-0.63	Early Failure
20	Peginterferon Alfa 2A	163	111.00	37.50-190.00	153.06	128.23-182.70	0.92	0.83-1.02	Random Failure
21	Axitinib	89	69.00	21.00-156.00	119.16	88.17-161.05	0.73	0.62-0.85	Early Failure
22	Imatinib	82	168.50	30.00-835.75	417.06	285.45-609.35	0.60	0.51-0.72	Early Failure
23	Paclitaxel	164	60.00	22.00-108.00	78.82	67.38-92.20	1.03	0.91-1.16	Random Failure
24	Pazopanib	128	25.00	10.00-49.00	48.73	37.00-64.18	0.67	0.59-0.75	Early Failure
25	Pemetrexed	128	47.00	21.00-151.00	106.27	85.79-131.65	0.86	0.76-0.97	Random Failure
26	Cyclophosphamide	78	51.50	3.25-107.25	75.53	46.50-122.69	0.49	0.41-0.57	Early Failure
27	Everolimus	85	56.00	13.00-131.00	110.03	74.47-162.56	0.58	0.50-0.67	Early Failure
28	Ibrutinib	52	205.50	21.00-735.00	331.32	206.23-532.27	0.60	0.48-0.75	Early Failure
29	Doxorubicin	20	12.50	8.00-79.00	42.46	22.58-79.85	0.74	0.53-1.03	Early Failure
30	Nilotinib	74	173.50	32.75-711.25	345.46	237.62-502.25	0.64	0.54-0.77	Early Failure

4 Discussion

Endocrine toxicity is a common adverse reaction associated with anti - neoplastic drug therapy; however, there is currently a lack of large - scale studies investigating the potential relationship between anti - neoplastic drugs and endocrine toxicity. This study extracted data from the FAERS database to identify anti - neoplastic drugs associated with endocrine toxicity. Immune checkpoint inhibitors accounted for the highest proportion of case reports, with the majority of reports originating from the United States and Japan. Demographic analysis indicated that the majority of adverse events (AEs) involved females, with the highest proportion of AEs occurring in patients aged 18–64.9 years, with a median age of 57 years. In terms of timing, 44.54% of events occurred within 1 month of treatment initiation. Notably, life - threatening outcomes or death were recorded in 13.75% of cases.

The present study demonstrated that female patients exhibited a significantly higher incidence of chemotherapy - related endocrine toxicity relative to male counterparts. Consistent with previous evidence, female patients are known to carry an elevated risk of endocrine adverse events across multiple classes of anti - neoplastic agents, especially thyroid dysfunction and hypogonadism triggered by immune checkpoint inhibitors and conventional cytotoxic chemotherapies [19]. Findings from large - scale real - world data analyses and clinical trials further confirmed that females receiving ICI therapy are at substantially increased risk of hypothyroidism, thyroiditis, and hypophysitis compared with males. Such gender - based disparities may be attributed to intrinsic biological characteristics of the female immune system; females generally display more robust humoral and cellular immune reactivity, which may potentiate anti - neoplastic effects but simultaneously raise susceptibility to autoimmune - mediated endocrine injury [20, 21]. Gender also modulates endocrine toxicity profiles associated with conventional cytotoxic agents. Females undergoing platinum - based chemotherapy demonstrate higher rates of ovarian failure and premature menopause, which may be explained by the greater sensitivity of ovarian follicular reserve to DNA - damaging agents and prolonged drug half - life observed in female patients [22]. Targeted anti - neoplastic agents also display a sex - dependent profile of endocrine adverse effects. In patients with advanced gastroenteropancreatic neuroendocrine tumors receiving sunitinib and similar drugs, the incidence of hypertension and thyroid dysfunction is notably higher in females than in males. This disparity potentially stems from sex - related variations in CYP450 enzyme expression and pharmacokinetic differences arising from divergent body compositions [23]. Regarding age distribution, anti - neoplastic drug - related adverse events are most frequently observed in the population aged 18–64.9 years. Previous evidence indicates that older age is positively linked to heightened toxicity risk during anti - neoplastic therapy, mainly due to physiological reserve diminution and altered drug handling with aging [7]. Nevertheless, although aging elevates the risk of dose - limiting toxicities, available data suggest that such risks remain within acceptable limits in Phase I trials, and elderly participants have not been systematically precluded from high - dose cohorts [24].

Our analysis revealed that over 50% of endocrine toxicities developed within the first two months of treatment initiation, indicating that these events predominantly cluster in the early therapeutic window. While the temporal patterns were broadly concordant across drug categories, subtle disparities were evident upon closer examination. Immune checkpoint inhibitors characteristically produced endocrine toxicity between 7 and 24 weeks, with onset timing varying by the specific endocrine organ affected. Conversely, traditional cytotoxic drugs and hormonal agents were associated with delayed emergence of endocrine complications, displaying a wear - out failure profile characterized by gradually accumulating risk as treatment duration extended [25, 26]. The present study identified significant disparities in TTO of endocrine toxicity between male and female patients, as well as between cases with fatal versus non - fatal clinical outcomes. Gender - dependent modulation of the hypothalamic - pituitary - gonadal axis may contribute to differential susceptibility to radiation or chemotherapy - induced endocrine damage. Given that female gonads generally display greater radiosensitivity compared with male gonads, female patients may develop hypogonadism at lower cumulative doses or within a shorter exposure interval. Sexual dimorphism in body fat distribution may also modify the pharmacokinetic profile and tissue concentration - time curve of anti - neoplastic agents within target endocrine organs, thereby indirectly influencing the TTO of endocrine adverse events. Notably, TTO for life - threatening or fatal endocrine toxicity is typically shorter and frequently involves impairment of the hypothalamic - pituitary - adrenal axis or myxedema coma secondary to severe hypothyroidism, which is closely associated with the functional physiological reserve of the affected endocrine axis [27]. Collectively, these findings highlight the importance of gender and severity - stratified clinical monitoring. To mitigate the risk of fatal adverse events, earlier and more frequent surveillance of endocrine function - with particular emphasis on adrenal axis integrity-is warranted in high - risk patient populations.

Further subgroup analysis demonstrated that immune checkpoint inhibitors exhibited the highest ROR values and incidence rates. As of July 2026, one approved immune checkpoint inhibitor (ipilimumab) had been assigned a black box warning for endocrine toxicity, while seven other drugs (navolumab, pembrolizumab, simiplimab, dostarlimab, atezolizumab, duvalirumab, and avirumab) included warnings regarding endocrine toxicity in their prescribing information.

Ipilimumab, a monoclonal antibody targeting CTLA – 4, was the first approved CTLA – 4 inhibitor and represents a milestone in the field of cancer immunotherapy. However, its mechanism of immune activation also gives rise to a unique spectrum of toxicities, with endocrinopathy being one of the most common and challenging adverse reactions. During treatment with ipilimumab, the incidence of immune - related endocrine adverse events is approximately 3.5% – 8% [28], although considerable variation exists across different studies and clinical settings. Data indicate that the incidence of endocrine adverse events is relatively low with ipilimumab monotherapy, whereas combination therapy significantly increases the risk [29]. Hypopituitarism and thyroid dysfunction represent the endocrine toxicities most commonly linked to ipilimumab, each with an incidence of over 10%. Mechanistically, these side effects are driven primarily by an “off - target” action, through which the antibody binds directly to CTLA – 4 antigens expressed aberrantly on non - immune cell populations [2]. Interestingly, endocrine toxicity may serve as a positive prognostic indicator for treatment response. A comparative study found that 45% of patients with endocrine adverse events attained satisfactory tumor responses, versus 28.3% of those without such events ($p = 0.002$); moreover, the endocrine toxicity group showed markedly prolonged overall survival ($p < 0.001$) [30]. Current guidelines advocate periodic monitoring of adrenocorticotrophic hormone (ACTH) and thyroid - stimulating hormone (TSH) levels during ipilimumab administration. However, retrospective evidence suggests that abnormal test results from routine screening are often difficult to interpret accurately, and that early recognition of toxicity not identified by standard assays still demands considerable clinical alertness [31, 32]. FDG - PET/CT has shown promise in detecting immune - related endocrine abnormalities, but FDG - PET evaluation is limited in patients receiving high - dose glucocorticoids [33]. The cornerstone of managing endocrine toxicity is hormone replacement therapy and symptom control; in clinical practice, thyroxine and cortisol replacement therapy are frequently required. Whether high - dose corticosteroids are necessary to treat endocrine abnormalities and preserve endocrine function remains to be further studied. Discontinuation of ipilimumab may also be necessary in the event of severe (Grade 3) adverse events [2]. The above findings suggest that a multimodal assessment strategy (combining serum biochemical markers, imaging studies, and clinical evaluation) may be a key approach to optimizing the early identification and management of endocrine toxicity.

Multivariate analysis further indicated that cytotoxic drugs (carboplatin, pemetrexed), immune checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab, atezolizumab, durvalumab), molecularly targeted therapies (lenvatinib, cabozantinib, sunitinib, axitinib, pazopanib), and monoclonal antibodies (alemtuzumab, bevacizumab) are all risk factors for drug - related endocrine toxicity.

Our findings demonstrated that molecularly targeted agents represent a major contributor to endocrine toxicity among anti - neoplastic therapies. Lenvatinib is a multitargeted tyrosine kinase inhibitor approved for the management of multiple solid malignancies, including hepatocellular carcinoma, thyroid carcinoma, and renal cell carcinoma. The inhibitory activity of lenvatinib against vascular endothelial growth factor receptors (VEGFRs) is closely implicated in the modulation of endocrine homeostasis, with thyroid dysfunction representing one of the most characteristic endocrine adverse events associated with this agent. Preclinical investigations and clinical observations have consistently indicated that the VEGFR signaling axis is indispensable for preserving the normal function of thyroid follicular cells. Blockade of this signaling cascade may trigger structural and functional impairment of the thyroid capillary microvasculature, thereby disrupting thyroid hormone biosynthesis and secretion. This mechanism is believed to represent a key pathogenic event underlying lenvatinib - induced hypothyroidism [34]. In this study, among the 33 patients who developed hypothyroidism, 27 (84.4%) experienced onset within the first 2 weeks of lenvatinib therapy. Notably, patients with hypothyroidism had significantly prolonged progression free survival (anti - neoplastic) compared with those without this adverse event. A plausible explanation is that hypothyroidism may serve as an indirect biomarker of adequate target inhibition, reflecting sufficient drug exposure and effective target coverage achieved by lenvatinib in vivo. Moreover, thyroid function might modulate the tumor microenvironment and immune surveillance, thereby indirectly influencing anti - neoplastic efficacy. These observations suggest that mild - to - moderate hypothyroidism should not be overinterpreted as a toxicity warranting aggressive intervention; nevertheless, the impact of thyroid hormone replacement on patients’ quality of life must be

carefully balanced [35]. Consequently, a comprehensive baseline thyroid function evaluation - encompassing TSH, FT4, FT3, and thyroid autoantibodies - is recommended prior to treatment initiation to exclude pre - existing thyroid disorders. Post - treatment monitoring should be performed at weeks 1, 2, 4, and 8, after which the testing interval may be appropriately extended, and levothyroxine supplementation can be administered when clinically indicated.

As a foundational class of anti - neoplastic therapeutics, cytotoxic agents have been integral to cancer management for decades; concurrently, the endocrine toxicities attributable to these drugs have attracted escalating investigative attention. Carboplatin functions primarily by disrupting DNA synthesis and impeding cell division. Available data indicate that carboplatin does not exert direct cytotoxicity against endocrine glands; rather, the tissue damage and attendant inflammatory responses elicited by this agent may reshape the immunological milieu. Additionally, the apoptotic death of tumor cells induced by cytotoxic therapy releases abundant autoantigens, thereby compromising immune tolerance. Subsequent programmed cell death protein - 1 (PD - 1) blockade disengages these immunological checkpoints, potentially unleashing autoimmune responses directed against endocrine tissues. Consequently, carboplatin may serve as an indirect facilitator of endocrine toxicity by enhancing antigen presentation and sensitizing the immune system to subsequent autoimmune activation following checkpoint blockade [36]. Although evidence that carboplatin, as a chemotherapeutic agent, directly causes endocrine toxicity is limited, relevant studies suggest that patients may exhibit signs of hyperthyroidism during carboplatin-based chemotherapy, even if left untreated, and that subsequent immunotherapy triggers a marked shift in thyroid function. This highlights the importance of systematic monitoring and standardized management of thyroid function in combination regimens that include carboplatin - based chemotherapy and immunotherapy [37].

Cabozantinib and sunitinib are two important targeted therapies for the treatment of renal cell carcinoma (RCC). Cabozantinib is a multi - targeted tyrosine kinase inhibitor that targets signaling pathways such as the mesenchymal - epithelial transition factor (MET), anexelekto (AXL), and VEGFR; Sunitinib, on the other hand, is a traditional VEGFR inhibitor that has long served as the standard of care for advanced renal cell carcinoma. Both drugs are known to cause thyroid dysfunction, and thyroid function must be closely monitored during treatment [38]. In the PIVOT - 09 trial, a comparative study of bepegaldesleukin combined with nivolumab versus a TKI (sunitinib or cabozantinib) showed that the incidence of grade 3/4 treatment - related adverse events in the TKI group was 56.5%, significantly higher than the 25.8% observed in the immunotherapy combination group [39]. The occurrence of endocrine toxicity associated with cabozantinib and sunitinib is closely related to their kinase inhibition profiles. Cabozantinib targets multiple signaling pathways, including MET, AXL, and VEGFR, while sunitinib primarily inhibits VEGFR. These targets are not only involved in tumor angiogenesis but also play important roles in the physiological functions of normal endocrine organs (such as the thyroid) [40]. Exposure - response analysis showed that after reducing the cabozantinib dose from 40 mg to 20 mg, the hazard ratio (HR) for disease progression or death was 1.00 (95% CI: 0.78–1.27), indicating that appropriate dose adjustment does not compromise efficacy while reducing the risk of adverse events [41]. This finding has important implications for the management of endocrine toxicity: through individualized dose adjustments, the toxicological burden can be reduced without compromising efficacy.

Pembrolizumab is a humanized monoclonal antibody directed against PD - 1 that has exhibited substantial anti - neoplastic efficacy across a spectrum of malignancies. Nevertheless, while this agent enhances immune - mediated cytotoxicity against malignant cells, it concurrently predisposes patients to a range of irAEs, among which endocrine toxicities constitute a clinically significant concern [42]. Thyroid dysfunction represents the most frequently encountered endocrine toxicity associated with pembrolizumab therapy. A previously reported case described a patient who developed suppressed TSH levels four months following pembrolizumab initiation; notably, this individual tested negative for thyroid peroxidase (TPO) antibodies. The condition subsequently progressed to overt hypothyroidism, with the final diagnosis of drug-induced thyroiditis. This observation implies that the pathogenesis of ICI - associated thyroiditis may encompass alternative immunoregulatory mechanisms that operate independently of antibody - mediated destruction of thyroid tissue [43]. Beyond T - cell activation and immune homeostasis imbalance, alternative mechanistic hypotheses have been

proposed to explain the pathogenesis of endocrine toxicity in relevant investigations. Clinical evidence derived from cases of hypoparathyroidism indicates that localized inflammatory reactions within endocrine target organs may represent a critical underlying mechanism. Notably, in patients with severe colitis, administration of intensive immunosuppressive therapy can restore parathyroid hormone (PTH) concentrations to normal ranges; conversely, tapering of immunosuppressive agents is often accompanied by a secondary reduction in PTH levels [44]. Accordingly, routine monitoring of thyroid function and comprehensive evaluation of other endocrine axes are clinically imperative for individuals undergoing pembrolizumab therapy. For patients exhibiting clinical manifestations including fatigue, cold intolerance, anxiety, and heat intolerance, the possibility of thyroid dysfunction should be thoroughly evaluated. Clinical management strategies should be individually optimized according to the specific subtype and severity of endocrine toxicity. In cases of hypothyroidism, levothyroxine replacement is recommended, whereas hormone substitution therapy may be necessary for the management of hypophysitis [45].

The strengths of this study include its long study period, large sample size, and standardized data cleaning process. We comprehensively employed various analytical methods, including the ROR test, PRR analysis, and logistic regression, to enhance the reliability of signal detection; at the same time, we validated the robustness of our conclusions through subgroup analysis and sensitivity analysis. However, this study also has some limitations. First, reporting bias and data incompleteness are concerns. FAERS is a spontaneous reporting system and is subject to inherent reporting bias. Underreporting is a widespread issue, particularly for mild endocrine toxicity that is well - recognized by clinicians, for which the reporting rate may be significantly lower than the actual incidence; some newer anti - neoplastic drugs have been on the global market for a relatively short time, resulting in relatively incomplete safety monitoring data. Furthermore, key information is often missing from reports, such as dosage, administration regimen, and patient comorbidities factors that are crucial for accurately assessing the risk of endocrine toxicity [46]. Second, the establishment of a definitive causal inference remains unattainable within the framework of this study. As the primary objective of FAERS - based pharmacovigilance analysis is to detect statistical signals and potential associations, such observational data are inherently insufficient to validate causal relationships; conclusive evidence of causality must be verified through well - designed prospective clinical investigations. Notably, adverse event reports implicating a given anti - neoplastic agent in endocrine toxicity may be confounded by the patient's underlying malignant condition, concurrent polypharmacy, or other uncharacterized confounding variables [47]. The disproportionality analysis employed in this study is only capable of generating quantitative signals for statistical correlation, and such findings do not necessarily confirm a direct causal link between the administered anti - neoplastic drugs and the reported endocrine adverse events. Finally, this study is limited by the challenges inherent in adjusting for confounding factors and performing robust subgroup analyses. Although stratification by age, gender, and other demographic variables was performed, the FAERS database possesses inherent constraints in controlling for complex confounders. Several critical prognostic and pathophysiological factors - including hepatic and renal function, genetic predisposition, and prior anti - neoplastic treatment history-are either incompletely documented or difficult to standardize within the database [46]. Accordingly, the potential risk factors identified from FAERS should be interpreted as preliminary and exploratory in nature, and further confirmation is warranted through large - scale epidemiological investigations or prospective clinical trials.

5 Conclusion

This study is, to our knowledge, the first to systematically evaluate anti - neoplastic drug - related endocrine toxicity using the FAERS database. Among 300 drugs with significant toxicity signals, 28 lacked endocrine warnings in their product labels. The median time to onset differed significantly by sex (52 days in males vs. 60 days in females) and by outcome severity (35 days in fatal vs. 59 days in non - fatal cases). Furthermore, Weibull analysis classified 17 of the top 30 drugs as early failure type, indicating highest toxicity risk at treatment initiation. In conclusion, our findings provide critical evidence for the clinical management and prevention of anti - neoplastic drug - induced endocrine toxicity. However, given

the inherent limitations of spontaneous reporting and signal detection methods, these results require validation through prospective pharmacoepidemiological studies with comprehensive causal assessments.

Declarations

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Author contributions

All members of this article participated in the first draft of the article. Xingnong Xu is responsible for study design, literature search and writing of the article. Cheng Fan is responsible for data extraction and data analysis. Xiaofeng Cheng is responsible for verification of data and revision of the manuscript. Both authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable.

Generative AI statement

During the preparation of this work, the authors used AI for linguistic polishing, sentence rephrasing and grammar consistency improvement. The authors fully reviewed, revised and edited all AI-assisted content, and take full responsibility for the integrity, accuracy and originality of this manuscript.

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Figures

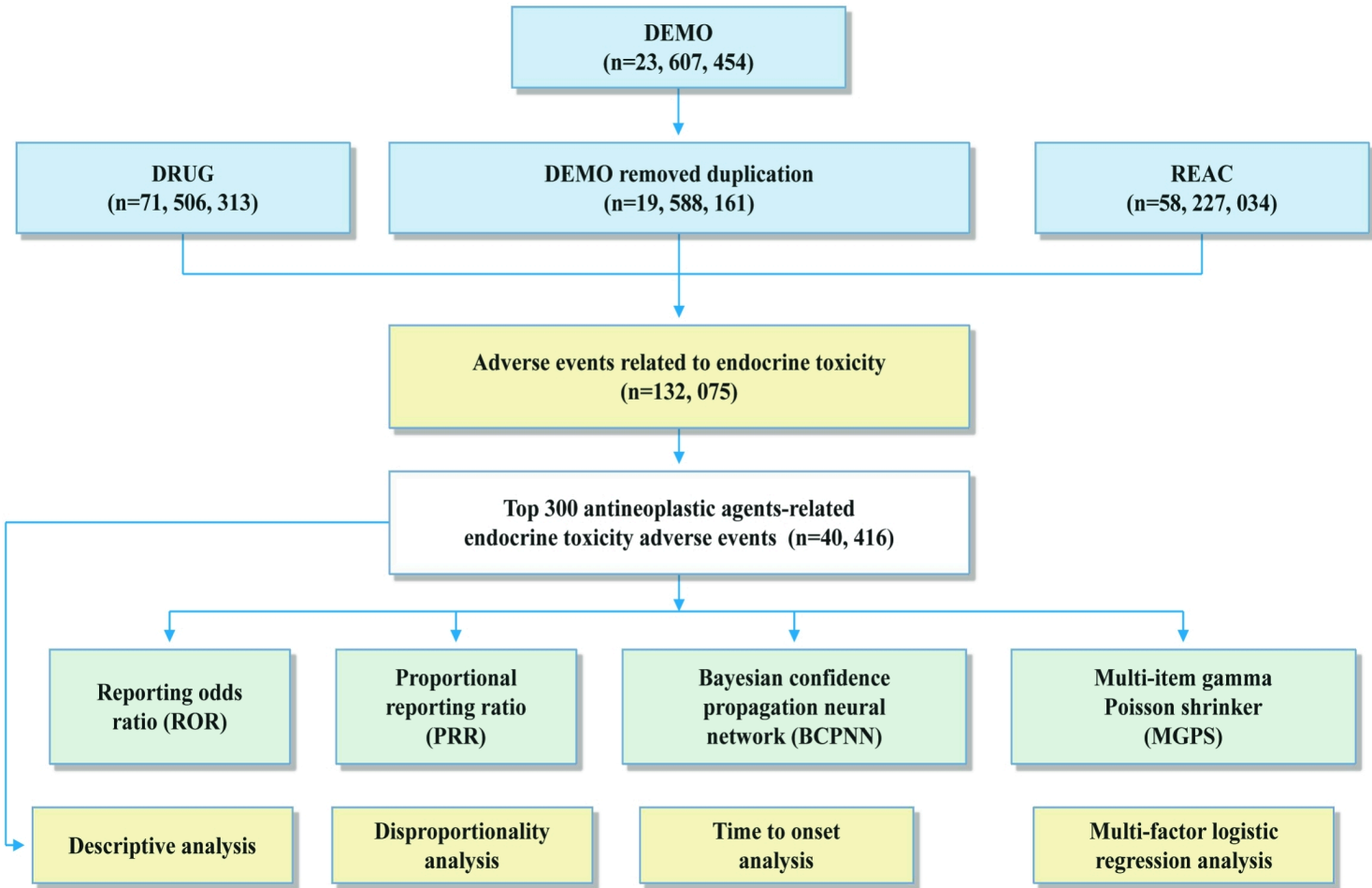


Figure 1

Flow diagram depicting data extraction and cleaning

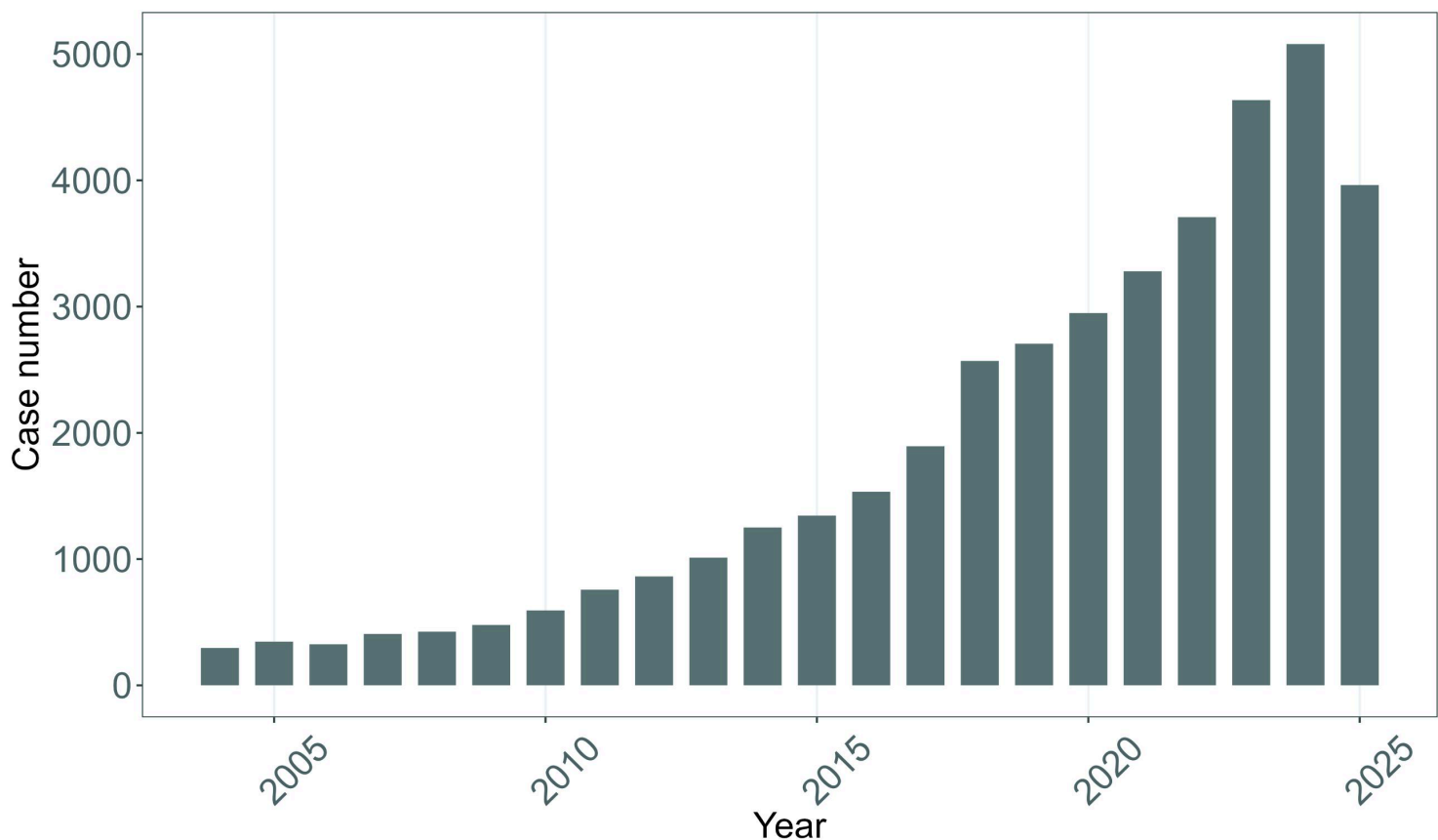


Figure 2
Number of annual reports.

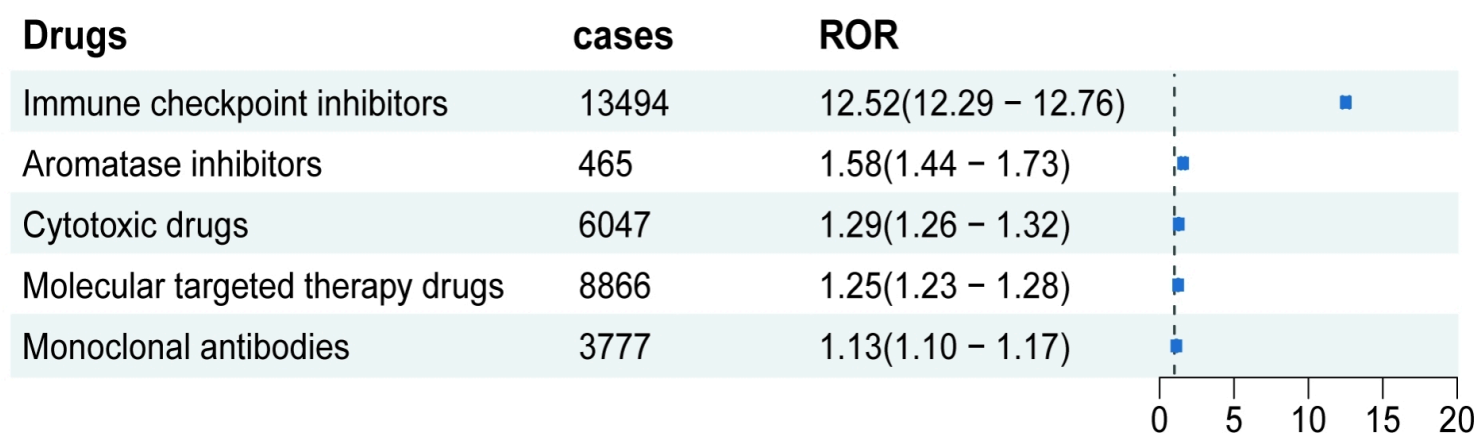


Figure 3
Forest plot of ROR values for different type of anti - neoplastic agents associated with endocrine toxicity in the FAERS database.

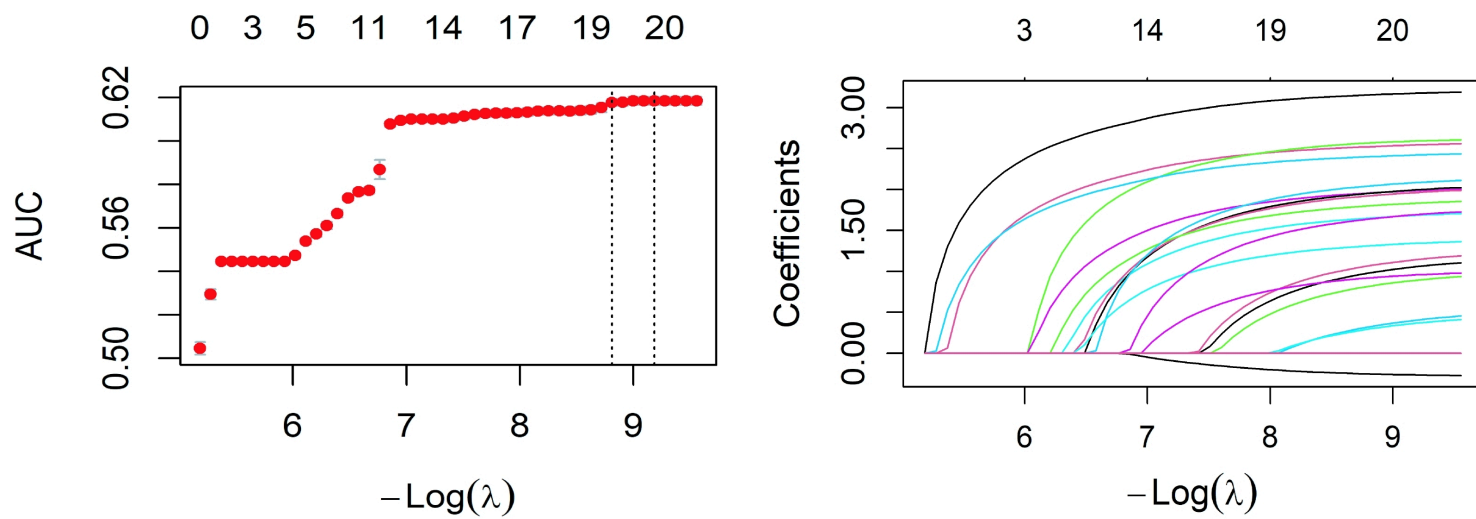


Figure 4

Results of LASSO regression analysis. LASSO, least absolute shrinkage and selection operator.

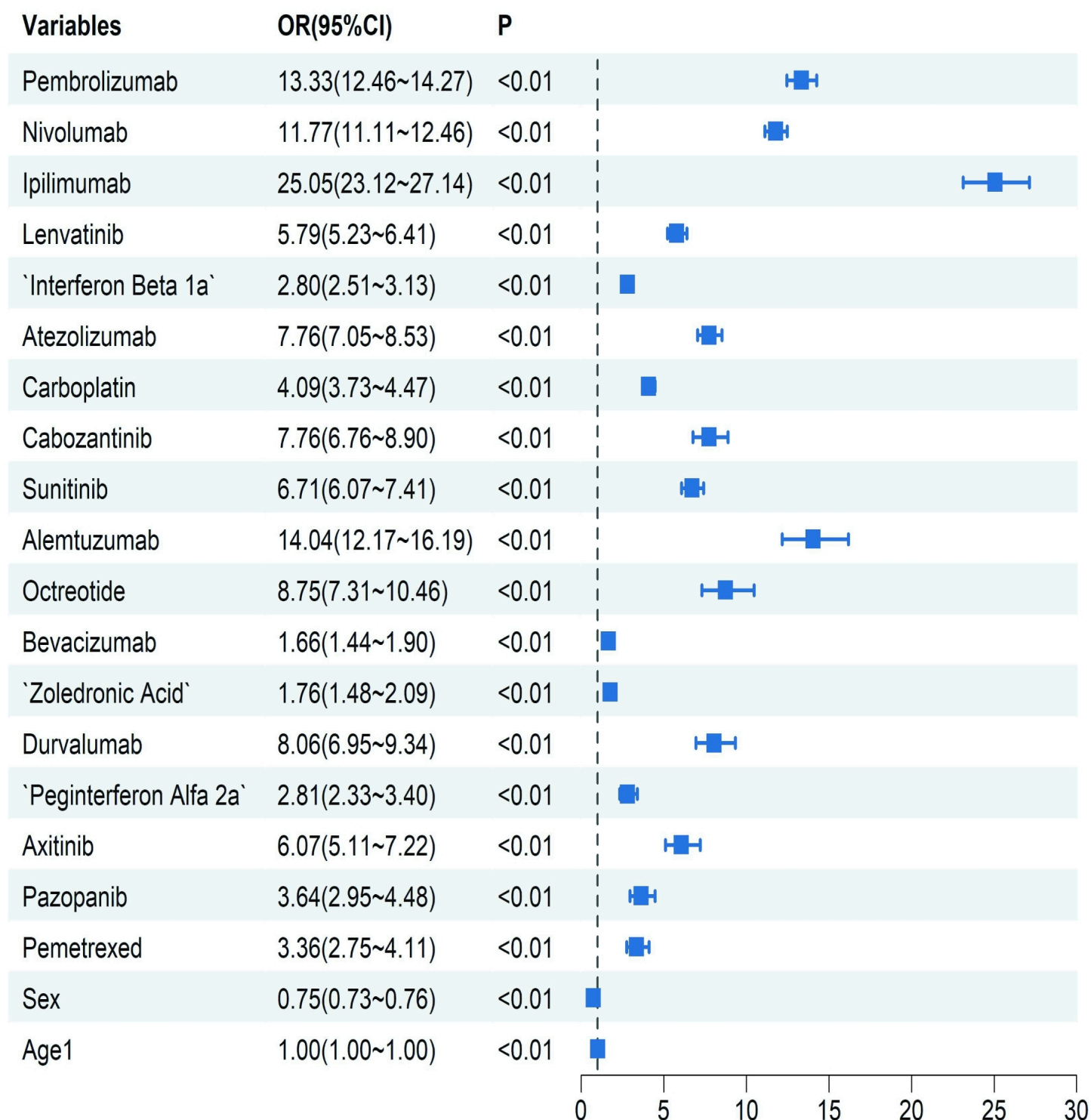


Figure 5

Results arising from multi - factor logistic regression analysis. CI, confidence interval; OR, odds ratio; P - adjust, p - value after Bonferroni correction; p - adjust < 0.01, statistically significant.

Distribution of time to onset

Left: percentage of reports | Right: number of reports

Percentage (%) Case number

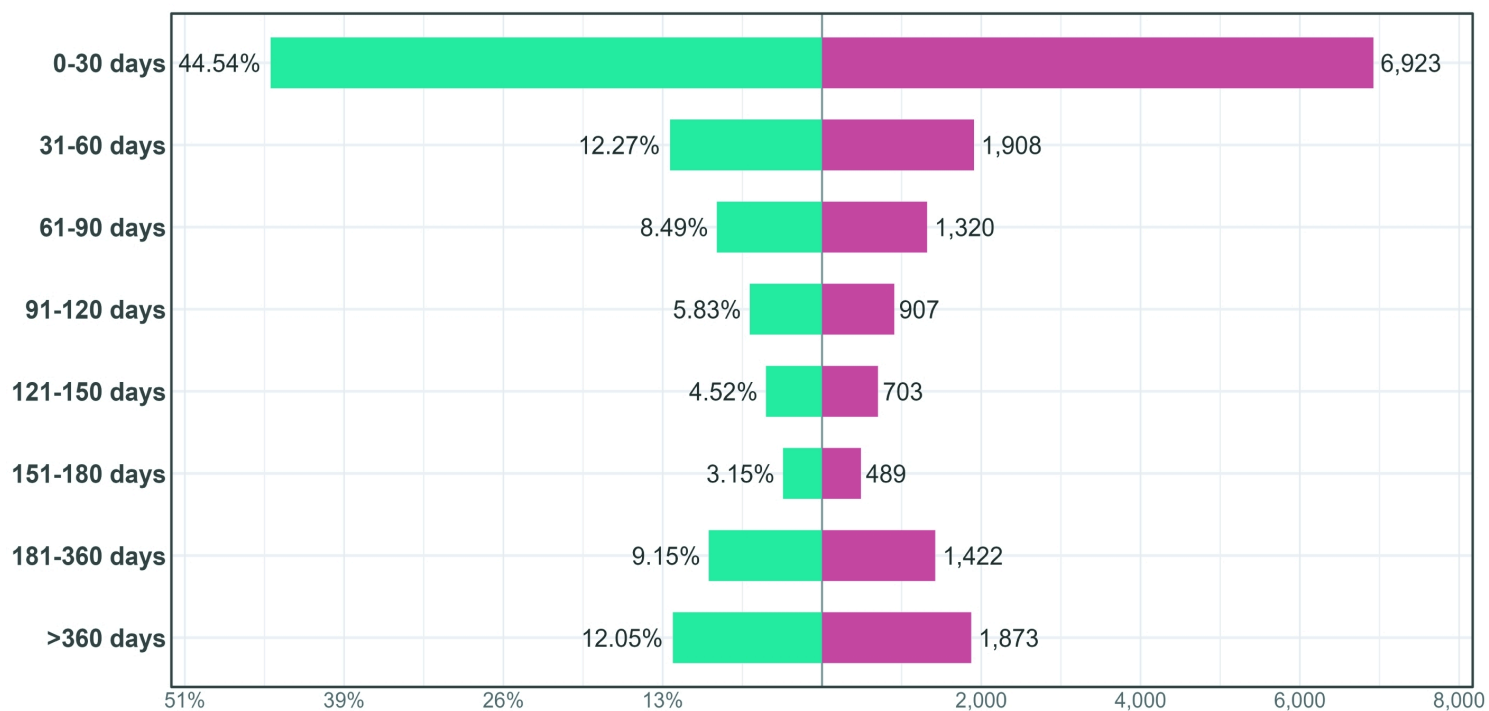


Figure 6

TTO of anti - neoplastic associated endocrine toxicity.

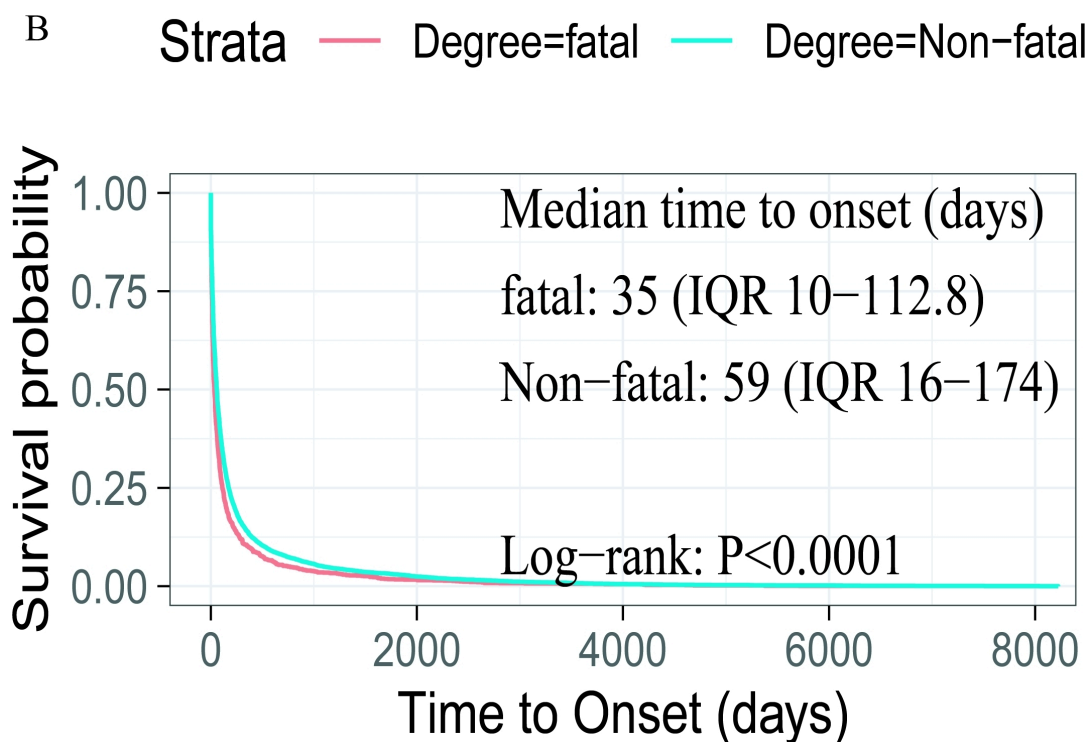
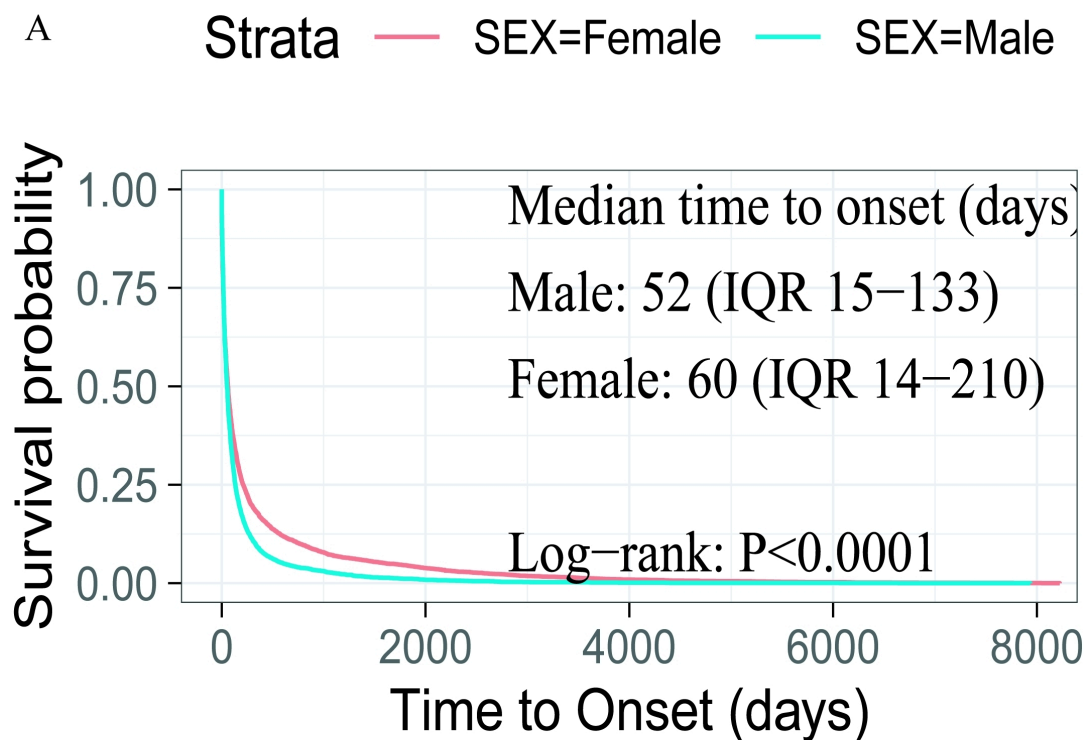


Figure 7

Kaplan - Meier curves for the TTO of anti - neoplastic - related endocrine toxicity in different subgroups. (A) Sex stratification. (B) Fatal event status. Inter - group statistical significance was assessed via the Kaplan - Meier analysis with log - rank tests.