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Original Article

Incidence and risk assessment of thyroid dysfunction following immune checkpoint inhibitor therapy: a systematic review and meta-analysis

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Abstract: Background: Immune checkpoint inhibitors (ICIs) have significantly enhanced the clinical outcomes for cancer patients. Nevertheless, they may be associated with the occurrence of ICI-associated thyroid dysfunction (ICI-TD). This study aimed to assess the risk of thyroid dysfunction in patients receiving ICI therapy. Methods: We systematically searched the PubMed, Embase, and Cochrane Library databases for phase II/III randomized controlled trials (RCTs) evaluating the use of ICIs in malignant tumors. The statistical analyses were conducted using Stata (version 17), and the risk of bias was assessed using Review Manager (version 5.4). Results: In total, 40 RCTs encompassing 12,376 patients were included. A higher relative risk (RR) of all-grade hyperthyroidism (RR = 9.91, 95% CI: 5.80-16.94; P < 0.01) was observed compared to hypothyroidism (RR = 7.70, 95% CI: 4.88-12.17; P < 0.01). Subgroup analyses indicated that combination ICI therapy was associated with a significantly higher incidence of ICI-TD than monotherapy. Among combination regimens, the PD-L1 combined with CTLA-4 group showed the highest risk of hypothyroidism (RR = 20.87, 95% CI: 5.07-85.81; P < 0.001), whereas the PD-1 combined with CTLA-4 group exhibited the highest risk of hyperthyroidism (RR = 17.34, 95% CI: 3.88-77.45; P < 0.001). Conclusion: ICI-associated hyperthyroidism was found to occur more frequently than hypothyroidism. Moreover, combination therapies significantly increased the incidence of ICI-TD.

Keywords: Immune checkpoint inhibitors, thyroid diseases, neoplasms, meta-analysis, incidence

Introduction

In recent years, immune checkpoint inhibitors (ICIs) have become a groundbreaking treatment for cancer patients. They work by interfering with the interaction between immune checkpoints and their ligands, thereby relieving immune suppression and reactivating T cells to fight tumors [1]. ICIs have demonstrated remarkable efficacy in treating various malignant tumors, including melanoma, non-small cell lung cancer, renal cell carcinoma, and hepatocellular carcinoma [2, 3]. Presently, three types of ICIs have been approved for solid tumor treatment: inhibitors of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), such as tremelimumab and ipilimumab; inhibitors of programmed cell death protein 1 (PD-1), including pembrolizumab, nivolumab, cemiplimab, camrelizumab, and sintilimab; and inhibitors of programmed cell death ligand 1 (PD-L1), like atezolizumab, avelumab, and durvalumab. Due to their mechanism of action in regulating the immune system, ICIs often lead to exces-

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sive T cell activation, which can cause unintended immune-related adverse events (irAEs) [4, 5].

Thyroid dysfunction is one of the most frequent irAEs, presenting as either hypothyroidism or hyperthyroidism [6]. The thyroid gland is particularly susceptible to immune-mediated damage due to its inherent vulnerability to the immune system [7]. Thyroid dysfunction caused by ICI therapy, termed ICI-associated thyroid dysfunction (ICI-TD) [8], is both prevalent and insidious, significantly affecting patient quality of life and compromising the sustainability and efficacy of antitumor therapies [9].

Despite its clinical importance, there are few systematic meta-analyses assessing the risk of thyroid dysfunction in patients treated with ICIs. Most studies on ICI-TD are single-center or small-sample investigations, limiting the generalizability of their results and introducing significant heterogeneity. This has led to uncertainty about the incidence and risk factors associated with ICI-TD. With separate risk assessments for hypothyroidism and hyperthyroidism, subgroup analyses by treatment regimen and tumor type, and the addition of follow-up time and diagnostic concordance assessment, this study aims to provide a comprehensive and systematic evaluation and meta-analysis of the risk of thyroid dysfunction in cancer patients treated with ICIs. The ultimate goal is to reduce the risk of thyroid dysfunction and improve the prognosis and quality of life of these patients.

Methods

This systematic review and meta-analysis adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. The study protocol was registered with PROSPERO (CRD42024613876).

The literature search strategy was designed to systematically identify studies examining the risk of developing thyroid dysfunction (TD) in patients with cancer following ICI treatment. Searches for English-language literature were conducted in PubMed, Embase, and the Cochrane Library databases. The study restricted the search to English-language literature. Search terms encompassed variations of thyroid dysfunction, including standard and code names for ICIs. Boolean operators were applied to combine keywords effectively and minimize irrelevant results. The search records are detailed in Supplementary Material. The databases were queried from their inception through October 2024. Full-text articles of the retrieved literature were subsequently reviewed to ensure the studies' relevance and quality.

Inclusion and exclusion criteria

This study established explicit inclusion and exclusion criteria to ensure the reliability and representativeness of the results.

Inclusion criteria: (i) The study population comprised patients with cancer, with no restrictions on cancer type or stage; (ii) The experimental group had received treatment with ICIs, including CTLA-4 inhibitors, PD-1 inhibitors, PD-L1 inhibitors, or combinations of these drugs; (iii) The control group had not received ICI treatment; (iv) Adverse events related to immune-related thyroid dysfunction had explicitly been reported; (v) The study type was a randomized controlled trial (RCT).

Exclusion criteria: (i) Studies that did not meet the specified study type, such as reviews, commentaries, or letters; (ii) Studies in which the experimental group had undergone combination treatments involving ICIs and other therapies (e.g., targeted therapies, chemotherapy, radiotherapy, or other immunotherapies). In cases of duplicate studies, the study with the longest follow-up period was selected for analysis.

Data extraction

In this study, two researchers (Li-Ying Wang and Yan-Jie Han) extracted the following data from the selected studies: ① basic information, including the lead author, publication year, trial phase, and study design type; ② patient characteristics, such as sample size, age, and tumor type; ③ detailed intervention information, including the type of immune checkpoint inhibitor (e.g., PD-1, PD-L1, CTLA-4 inhibitors), dosage, and administration frequency; ④ data related to thyroid dysfunction, including incidence and classification of TD (e.g., hypothyroidism, hyperthyroidism). In case of disagreement, consensus was reached after consulting with the third author (Min Li) regarding eligibility issues.

Risk of bias assessment

Assessing the risk of bias is a crucial step in ensuring the quality of this study. For randomized controlled trials, the Cochrane Risk of Bias Tool [11] will be used to evaluate seven aspects of bias, including selection bias, performance bias, and detection bias, among others, to identify potential risks in study design and implementation. The assessment outcomes will be employed to interpret the reliability of the meta-analysis results.

Statistical analyses

We utilized Stata software (version 17) for statistical analysis. For dichotomous variables, we calculated the relative risk (RR) and 95% confidence intervals separately, based on the number of events and non-events in both the intervention and control groups, to report the RR and its corresponding 95% confidence intervals. Heterogeneity among the included studies was primarily assessed using the I^2 statistic and the Q test. When heterogeneity was low ($P \geq 0.01$ or $I^2 < 50\%$), a fixed-effects model was employed; if heterogeneity was high ($P < 0.01$ or $I^2 \geq 50\%$), a random-effects model was used. Moreover, subgroup analyses and meta-regression were conducted to explore sources of heterogeneity, and sensitivity analyses were used to evaluate the robustness of the results. The Egger's test was applied to assess publication bias.

Results

Literature screening process

A search of English-language literature in PubMed, Embase, and Cochrane Library databases resulted in a total of 1,336 articles. After removing duplicates, we identified 1,041 articles. Of these, articles were excluded after reviewing titles and abstracts. Among the remaining 719 articles, we excluded 122 reviews, 99 meta-analyses, 126 case reports, and 37 conference abstracts. We further evaluated 335 articles, of which 10 did not mention thyroid-related immune-related adverse events, and 282 were related to the combination of immunotherapy with other regimens (e.g., chemotherapy, 124 radiotherapy, and targeted therapy). Additionally, three articles were excluded because the trials were ongoing. Finally, a total of 40 articles were included. The literature screening process is depicted in **Figure 1**.

Characteristics of the included studies

Table 1 summarizes the characteristics of the included studies. This study included 40 clinical trials involving 12,376 patients [12-51]. Among the monotherapy regimens, PD-1 inhibitor monotherapy was the most extensively studied, comprising 23 studies with 7,208 patients. Pembrolizumab monotherapy was the most prevalent, appearing in 18 studies involving 5,197 patients. Regarding combination regimens, the most common was PD-1 and CTLA-4 inhibitors, with seven studies and 1,926 patients. By cancer type, studies on non-small cell lung cancer were the most frequent (n = 15). According to the Cochrane Collaboration's tools for assessing risk of bias, the methodologic quality of the included trials was acceptable **Figure 2**.

Meta-analysis results

Overall meta-analysis results of hypothyroidism: In the meta-analysis of hypothyroidism, we included 40 studies with a total sample size of 12,376 cases. The results of the meta-analysis are depicted in **Figure 3**. The use of ICIs significantly elevated the risk of hypothyroidism in oncology patients compared to controls (RR = 7.70, 95% CI: 4.88-12.17, $P < 0.01$). In the heterogeneity analysis, significant heterogeneity was detected ($Q = 357.04$, $df = 39$, $P < 0.0001$, $I^2 = 89.1\%$); hence, a random-effects model analysis was conducted.

Subgroup analysis of the hypothyroidism group: To evaluate the risk of developing hypothyroidism based on various characteristics, this study performed subgroup analyses according to tumor types, types of ICIs, types of drugs, and experimental designs. Subgroup analyses were stratified according to these prespecified sources of potential heterogeneity. The DL random-effects model consistent with the overall meta-analysis was employed. Differences between the I^2 values within each subgroup and the overall I^2 value were compared to determine whether the factor contributed to heterogeneity.

In the tumor type subgroup analysis, the pleural mesothelioma group exhibited the highest risk

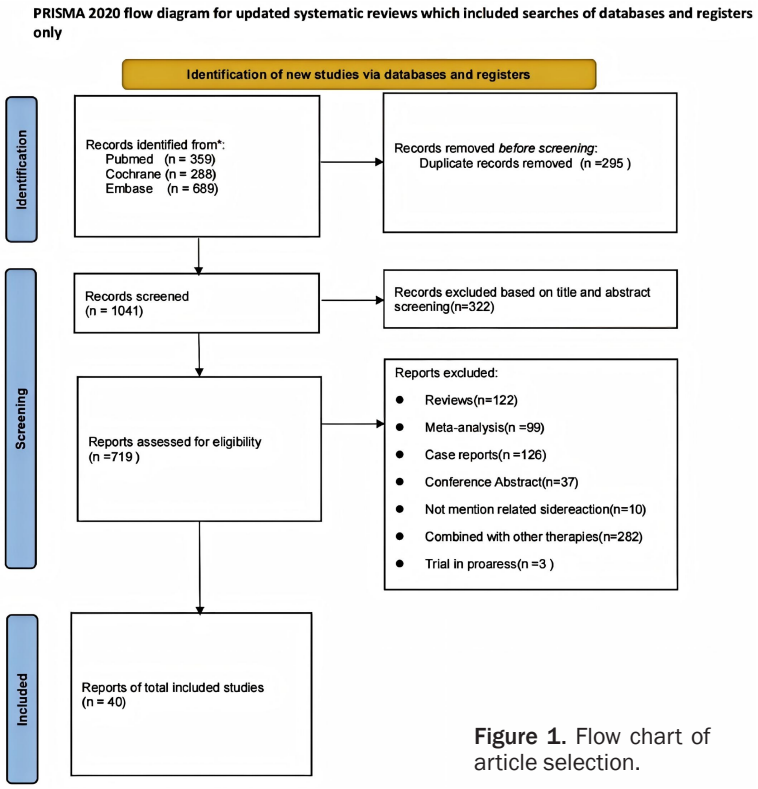

Figure 1. Flow chart of article selection.

of hypothyroidism following ICI treatment compared to the control group (I^2 = 0.0, RR = 71.25, 95% CI: 4.39-1157.05, P < 0.05). However, since only one study was included in this group, these findings should be interpreted with caution. The heterogeneity of the results in the renal cell carcinoma patient group was the highest, likely attributable to the variations in medication regimens and dosing regimens across the four studies (I^2 = 98.2%, RR = 3.82, 95% CI: 0.73-19.85, P < 0.001). The results are presented in Supplementary Material.

In the subgroup analysis of ICIs, we separately examined PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4 inhibitors to assess their distinct effects on hypothyroidism risk. The findings are illustrated in Supplementary Material. Regarding ICI type, we observed that the PD-L1 + CTLA-4 group had the highest incidence (RR = 20.87, 95% CI: 5.07-85.81, P < 0.001). Additionally, the combination of PD-1 and CTLA-4 showed a higher incidence (RR = 14.60, 95% CI: 2.54-83.94, P < 0.001). In contrast, the risk of hypothyroidism was lowest with the use of a PD-1 inhibitor alone (RR = 5.26, 95% CI: 3.75-7.37, P < 0.001). These results suggest that the risk of hypothyroidism is significantly increased when both ICIs are administered concurrently.

In the further subgroup analysis of specific drugs, we found that the highest risk of morbidity was in the group receiving Avelumab (RR = 22.57, 95% CI: 5.50-92.59, P < 0.001). However, since only one study was included in this group, this conclusion should be interpreted cautiously. The Durvalumab + Tremelimumab group ranked second in morbidity risk (RR = 20.87, 95% CI: 5.07-85.81, P < 0.001). Other drug classes with a higher risk of morbidity, in order, were the Atezolizumab group (RR = 20.50, 95% CI: 6.46-65.06, P < 0.001) and the Nivolumab + Ipilimumab group (RR = 15.68, 95% CI: 2.39-102.91, P < 0.001). In the Nivolumab + Ipilimumab group, the study by Motzer et al. (2018) clearly identified a source of heterogeneity. The results are depicted in Supplementary Material.

To investigate the source of heterogeneity, we conducted meta-regression analyses. Meta-regression analysis employed a mixed-effects meta-regression model (using REML estimation) with RR as the dependent variable and " tumor type, drug type, ICI type, and dosing design individually" as independent variables to quantify the explanatory power of each factor on heterogeneity. The results are displayed in **Table 2**, which show that tumor type (p = 0.631), drug type (p = 0.222), ICI type (p = 0.466), and dosing design (p = 0.420) were not the causes of the high heterogeneity.

Overall meta-analysis results of hyperthyroidism: In the meta-analysis of hyperthyroidism, we included 21 studies with a total sample size of 6,257 cases. The overall meta-analysis results are depicted in **Figure 4**.

The meta-analysis of hyperthyroidism revealed that the use of ICIs in oncology patients significantly increased the risk of developing hyperthyroidism compared to controls (RR = 9.91, 95% CI: 5.80-16.94, P < 0.01). In the heteroge-

Table 1. Characteristics of the included studies

Author	Study Year	Study design	Region	Immune checkpoint inhibitor	Control group
Ahn M J et al.	2023	Prospective	Korea	Durvalumab	Olaparib
Antonia S J et al.	2017	Prospective	America	Durvalumab	Placebo
Bajorin D F et al.	2021	Prospective	America	Nivolumab	Placebo
Bang Y J et al.	2017	Prospective	Korea	Ipilimumab	Best supportive care
Burtness B et al.	2019	Prospective	America	Pembrolizumab PD-1	Chemotherapy
Cho B C et al.	2024	Prospective	Korea	Pembrolizumab	EXTREME regimen
Cho B C et al.	2023	Prospective	Korea	Pembrolizumab	Bintrafusp alfa
Choueiri T K et al.	2021	Prospective	America	Pembrolizumab	Placebo
Chung H C et al.	2022	Prospective	Korea	Pembrolizumab	Paclitaxel
Cohen E E W et al.	2019	Prospective	America	Pembrolizumab	Standard-of-care therapy
De Castro G et al.	2023	Prospective	Brazil	Durvalumab + Tremelimumab	Standard chemotherapy
Di Giacomo A M et al.	2021	Prospective	Italy	Ipilimuma	Fotemustine
Doki Y et al.	2022	Prospective	Japan	Nivolumab + Ipilimumab	Chemotherapy
Eggermont A M M et al.	2015	Prospective	France	Ipilimumab	Placebo
Felip E et al.	2021	Prospective	Spain	Atezolizumab PD-L1	Best supportive care
Fennell D A et al.	2021	Prospective	UK	Nivolumab	Placebo
Ferris R L et al.	2020	Prospective	America	Durvalumab + Tremelimumab	Standard of care
Fradet Y et al.	2019	Prospective	Canada	Pembrolizumab	Chemotherapy
Fuchs C S et al.	2022	Prospective	America	Pembrolizumab	Paclitaxel
Galsky M D et al.	2020	Prospective	America	Pembrolizumab	Placebo
Grossmann K F et al.	2022	Prospective	America	Pembrolizumab + Ipilimumab	IFNα-2b
Hamanishi J et al.	2021	Prospective	Japan	Nivolumab	Chemotherapy
Kang Y K et al.	2017	Prospective	Nivolumab	Nivolumab	Placebo
Kojima T et al.	2022	Prospective	Korea	Pembrolizumab	Chemotherapy
Luke J J et al.	2022	Prospective	Poland	Pembrolizumab	Placebo
Merle P et al.	2023	Prospective	France	Pembrolizumab	Placebo
Mok T S K et al.	2019	Prospective	China	Pembrolizumab	Chemotherapy
Motzer R J et al.	2023	Prospective	America	Nivolumab + Ipilimumab	Placebo
Motzer R J et al.	2018	Prospective	America	Nivolumab + Ipilimumab	Sunitinib
O'brien M et al.	2022	Prospective	UK	Pembrolizumab	Placebo
Park S et al.	2022	Prospective	Korea	Durvalumab PD-L1	Placebo
Paz-Ares L G et al.	2022	Prospective	Spain	Nivolumab + Ipilimumab	Chemotherapy
Peters S et al.	2022	Prospective	Switzerland	Nivolumab + Ipilimumab	Observation
Peters S et al.	2022	Prospective	Switzerland	Nivolumab + Ipilimumab	Chemotherapy
Powles T et al.	2020	Prospective	UK	Avelumab PD-L1	Best supportive care
Powles T et al.	2022	Prospective	UK	Pembrolizumab	Placebo
Reck M et al.	2019	Prospective	Germany	Pembrolizumab	Chemotherapy
Ribas A et al.	2015	Prospective	America	Sintilimab PD-1	Chemotherap
Shitara K et al.	2020	Prospective	Japan	Sintilimab PD-1	Chemotherapy
Wang K et al.	2024	Prospective	China	Sintilimab PD-1	Active surveillance

neity analysis, moderate heterogeneity was observed (Q = 37.75, df = 20, P = 0.01, I^2 = 47.0%). Consequently, we conducted a random-effects model analysis.

Subgroup analysis of hyperthyroidism: Firstly, when analyzed by tumor type, patients with renal cell carcinoma had the highest risk of developing hyperthyroidism (RR = 43.43, 95% CI: 16.15-116.83, P < 0.01), based on 1,370 patients in the intervention group and 1,514 in the control group. Pleural mesothelioma was the second highest risk group, with a significantly lower risk than for renal cell carcinoma (RR = 29.07, 95% CI: 4.04-209.24, P < 0.001), though the sample size was relatively small

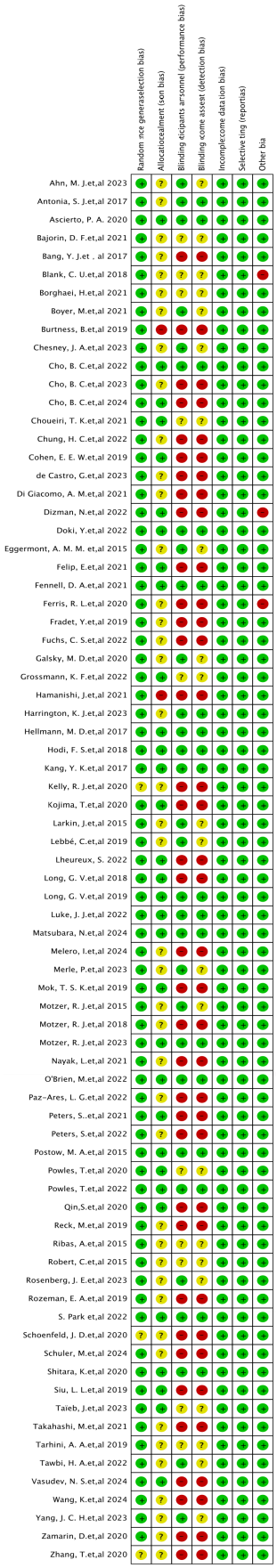

Figure 2. Deviation risk map on each domain.

(intervention group: 56; control group: 74). Additionally, the risk of developing hyperthyroidism in patients with urothelial carcinoma was also relatively high (RR = 11.93, 95% CI: 3.70-38.53, P < 0.001), with 600 patients in the intervention group and 620 in the control group. In contrast, esophageal cancer had the lowest risk of developing hyperthyroidism (RR = 5.63, 95% CI: 2.18-14.54, P < 0.01), with 328 patients in the intervention group and 161 in the control group, as shown in Supplementary Material.

The risk of hyperthyroidism is discussed based on the type of ICI. The specific results are presented in Supplementary Material. According to the findings, the highest risk of morbidity was observed in the group using PD-1 combined with CTLA-4 (RR = 17.34, 95% CI: 3.88-77.45, p < 0.001). This was followed by the PD-L1 combined with CTLA-4 group (RR = 15.92, 95% CI: 2.11-120.06, p < 0.05). Hence, it is clear that the combination of PD-1 and CTLA-4 poses a higher risk of hyperthyroidism.

When analyzed by drug class, the highest incidence was found with the combination of Durvalumab and Tremelimumab (RR = 35.53, 95% CI: 2.14-588.83, P < 0.001). The next highest risk of morbidity was observed in the group using Nivolumab in combination with Ipilimumab (RR = 15.10, 95% CI: 4.10-55.63, P < 0.01). This finding aligns with the results of the ICI subgroup analyses, further supporting the evidence of higher morbidity in patients with tumors treated with combination therapies. The specific results are presented in Supplementary Material.

Sensitivity analysis

To further evaluate the robustness and reliability of this meta-analysis, we conducted sensitivity analyses on the meta-results for the hypothyroidism and hyperthyroidism groups separately. The detailed results are presented in **Figures 5** and **6**.

In the meta-analysis of hypothyroidism, the pooled RR remained within the range of 4.48 to 12.16 after sequentially excluding each study, and all remained within the confidence interval. This indicates that the exclusion of any single

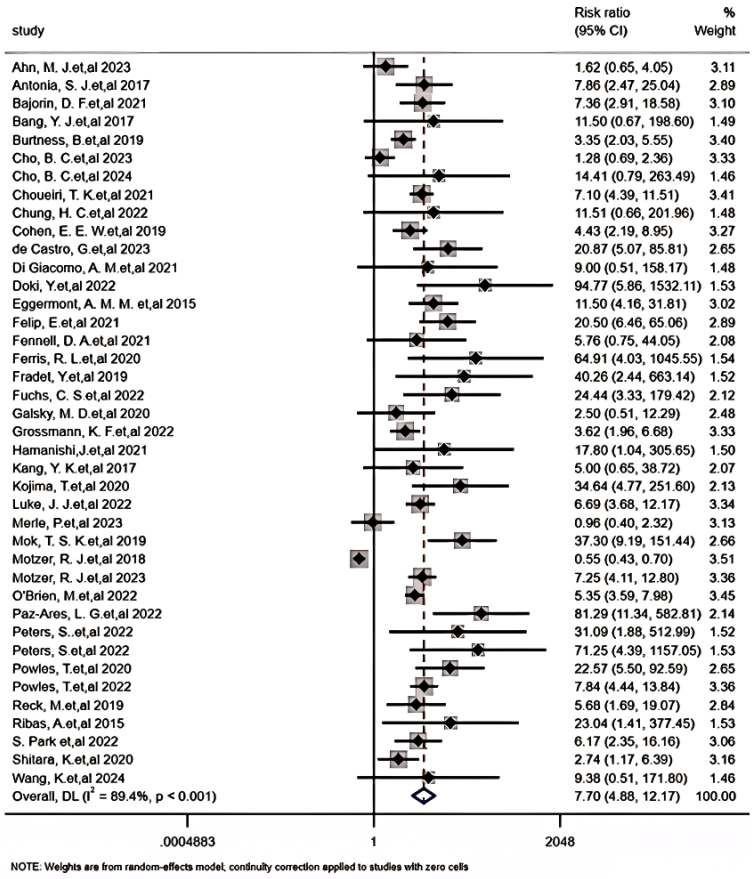

Figure 3. Meta results of hypothyroidism.

study had a minimal impact on the pooled RR, further confirming the stable risk estimates for hypothyroidism. The results are depicted in **Figure 5**. Similarly, a sensitivity analysis was conducted for the meta-analysis of hyperthyroidism. The findings revealed that after individually excluding each study, the pooled RR stayed between 5.80 and 16.94, all within the confidence interval, suggesting that the combined effect estimate for hyperthyroidism was stable and not substantially affected by any single study. **Figure 6** summarizes the results of the sensitivity analysis for hyperthyroidism.

These results indicate that the findings of this meta-analysis are relatively robust and do not vary significantly due to the inclusion of a single study.

Publication bias

To ensure that the meta-analysis results were not influenced by publication bias, we evaluated the included studies for publication bias using Egger's test to identify any trends of systematic bias. Egger's test results for the hypothyroidism meta-analysis showed p = 0.380, indicating that the meta-analysis of hypothyroidism did not exhibit any significant signs of publication bias.

In Egger's test for hyperthyroidism, the *p*-value was 0.264, which did not reach a significant level, further supporting the robustness of the meta-analysis results for hyperthyroidism. The non-significant outcome of Egger's test suggests that the included studies maintained reasonable objectivity and were not affected by systematic bias due to publication bias.

Discussion

Key findings

We systematically evaluated the risk of developing thyroid dysfunction (TD) in oncology patients who received immune checkpoint inhibitors (ICIs) through a meta-analysis. A total of 40 studies with a combined sample size of 12,376 cases were included. The results of this study indicated that the use of ICIs significantly increased the risk of developing TD in oncology patients. Firstly, concerning hypothyroidism, ICI treatment notably elevated its incidence, with a pooled risk ratio (RR) of 7.51, suggesting a strong association between ICI treatment and hypothyroidism. Among tumor types, patients with pleural mesothelioma had the highest risk of developing hypothyroidism, while those with renal cell carcinoma had the lowest risk. Notably, the risk of developing hyperthyroidism in patients with urothelial carcinoma was found to be significantly elevated (RR = 11.93, 95% CI: 3.70-38.53; P < 0.001). However, this result should be interpreted with caution. The total number of patients in this subgroup was relatively limited, with 600 patients in the experimental group and 620 in the control group. Although that sample size is not negligible, it may still intro-

Table 2. Results of the multiple regression analysis

Variable	Regression coefficient	Standard error	t-value	*p*-value	95% confidence interval	τ^2
Tumor types	-0.028	0.057	-0.48	0.631	(-0.143, 0.875)	0.985
Drug classes	-0.097	0.078	-1.24	0.222	(-0.254, 0.061)	0.909
Types of ICIs	0.144	0.196	-0.74	0.466	(-0.253, 0.541)	0.979
Medication design	0.430	0.528	-0.81	0.420	(-0.638, 1.498)	1.011

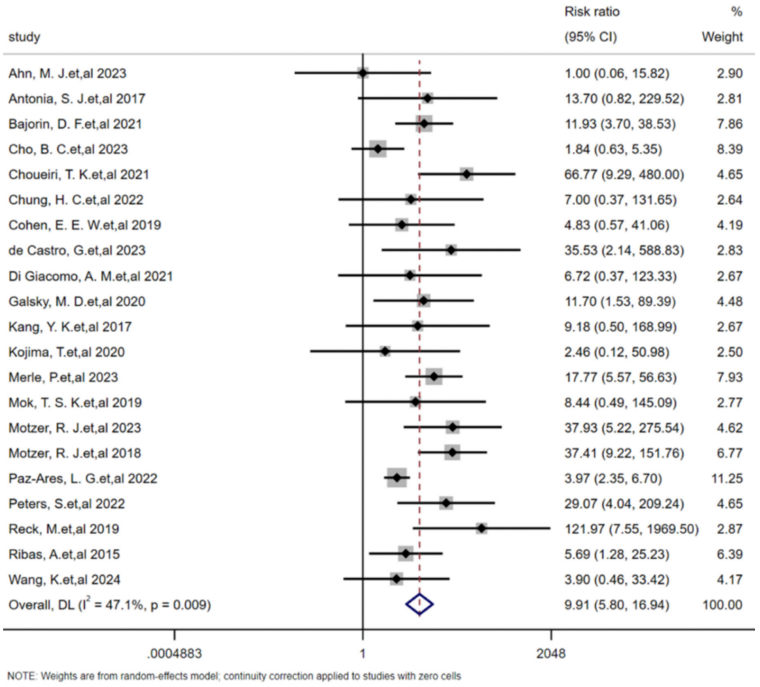

Figure 4. Meta results of hyperthyroidism.

duce statistical variability and contribute to the wide confidence intervals observed. Therefore, the high relative risk in this subgroup may, at least in part, reflect sample size effects rather than an actual increase in incidence. Further large-scale studies focusing specifically on thyroid irAEs in different cancer types, including urothelial carcinoma, are needed to validate this finding. Additionally, differences in cancer biology, treatment regimens, and patient characteristics may also contribute to the variability in immune-related thyroid dysfunction among different tumor types. Regarding ICI types, the lowest risk of morbidity was observed with PD-1 inhibitors. ICI treatment also raised the risk of hyperthyroidism in oncology patients, with a risk ratio (RR) of 9.91. Esophageal cancer patients had the lowest risk of developing hyperthyroidism. Conversely, when ICIs were applied in combination (e.g., PD-1 combined with CTLA-4 or PD-L1 combined with CTLA-4), the risk of developing both hypothyroidism and hyperthyroidism was significantly higher.

Additionally, subgroup analyses revealed that the impact of different ICI types, tumor types, and experimental designs on the risk of TD varied. The results of the sensitivity analysis and publication bias analysis indicated that this meta-analysis had good robustness and objectivity.

Comparison with existing literature

The primary findings of this study align with the majority of conclusions found in the existing literature. Previous research has indicated that ICI treatment can result in immune-related adverse events within the endocrine system, with thyroid dysfunction being especially prevalent [52-54]. Our study found that the risk of hypothyroidism (RR = 20.87, 95% CI: 5.07-85.81) and hyperthyroidism (RR = 15.92, 95% CI: 2.11-120.06) were both high when using PD-L1 combined with CTLA-4. The findings from Irfan Vardarli et al. indicate that the combined PD-L1 plus CTLA-4 therapy group exhibited higher risks of hyperthyroidism (RR = 11.62, CI: 3.63-37.24) and hypothyroidism (RR = 7.33, CI: 1.31-41.10) compared to the monotherapy group. This is consistent with our study results [55]. Furthermore, findings from Romualdo Barroso-Sousa et al. indicate that patients receiving combination therapy exhibited the highest incidence rates of both hypothyroidism and hyperthyroidism. Compared to those treated with ipilimumab alone, patients on combination therapy demonstrated a significantly higher risk of developing hypothyroidism (OR = 3.81, CI: 2.10-

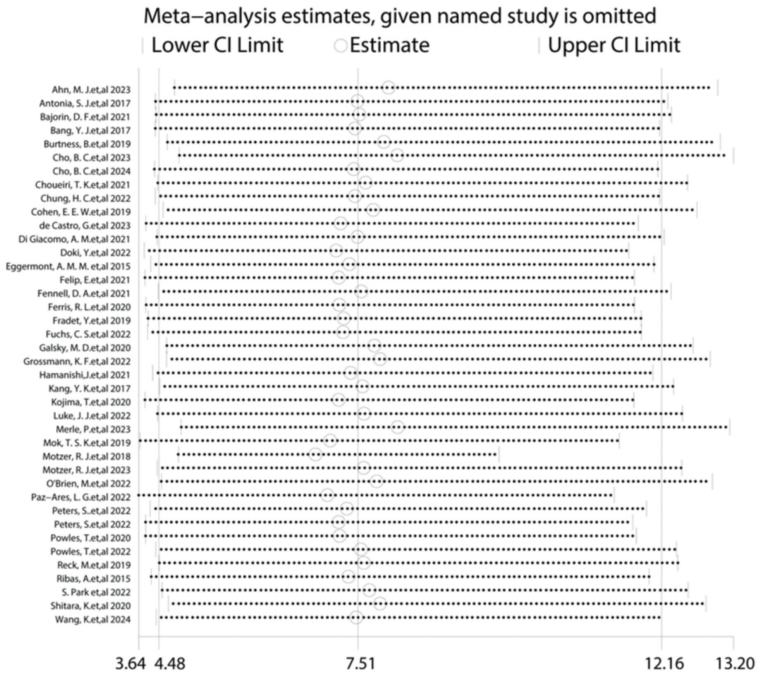

Figure 5. Sensitivity analysis (hypothyroidism group).

6.91) and hyperthyroidism (OR = 4.27, CI: 2.05-8.90) [6].

Additionally, there is some debate in the existing studies regarding the differences in the incidence of TD among various ICI types, which offers a reasonable explanation for the inconsistencies found in the literature. It is essential to consider the dynamic progression of ICI-TD when interpreting the findings of this meta-analysis. Although our pooled results showed a slightly higher incidence of hyperthyroidism compared to hypothyroidism, this trend is not entirely consistent with the findings of many individual studies or real-world clinical experience. In fact, in numerous studies, hyperthyroidism was identified as the initial manifestation of thyroid dysfunction, often without longitudinal follow-up to assess subsequent changes. It is well recognized that in patients receiving anti-PD-1 therapy, hyperthyroidism frequently represents an early, transient phase of ICI-TD that may later evolve into hypothyroidism over time. In our analysis, while most included studies did not provide detailed tracking of thyroid function over time, we found that the average follow-up duration reported in studies on hypothyroidism was 24.96 months (SMD = 12.96) and 24.24 months (SMD = 15.14) in studies on hyperthyroidism. Although the mean follow-up durations appear comparable between groups, the lack of consistent longitudinal assessments and standardized definitions of ICI-TD in the included studies limits the ability to capture the whole trajectory of thyroid dysfunction, particularly the transition from initial thyrotoxicosis to subsequent hypothyroidism. These limitations underscore the need for prospective studies with adequate follow-up period and more precise temporal classification of thyroid irAEs to define their incidence and clinical course more accurately. The results of this study are more comprehensive and robust compared to those of single-center or small-sample studies, improving the generalizability and representativeness of the findings.

Mechanism exploration

The mechanism by which ICIs induce thyroid dysfunction is not fully understood, but existing studies have proposed several explanations. T-cell-mediated cellular immunity seems to be the primary cause. Thyroid tissue is especially vulnerable to immune attack due to its high immune sensitivity [7]. Research has indicated that higher baseline levels of IL-10 can decrease the occurrence of thyroid dysfunction during PD-1 inhibitor treatment [56]. Blocking PD-1 suppresses the proliferation and differentiation of T regulatory cells (Tregs) [57], leading to their depletion and subsequent autoimmune thyroiditis [58]. Moreover, blocking the PD-1 and PD-L1 pathways can induce varying degrees of thyroid inflammation in different individuals, resulting in hypothyroidism or hyperthyroidism. These findings suggest that different immune checkpoint blockade pathways affect the thyroid differently, likely due to the degree of immune pathway activation and the specific targeting of thyroid cells. Lastly, thyroid dysfunction associated with ICIs may also be influenced by individual immune gene expression,

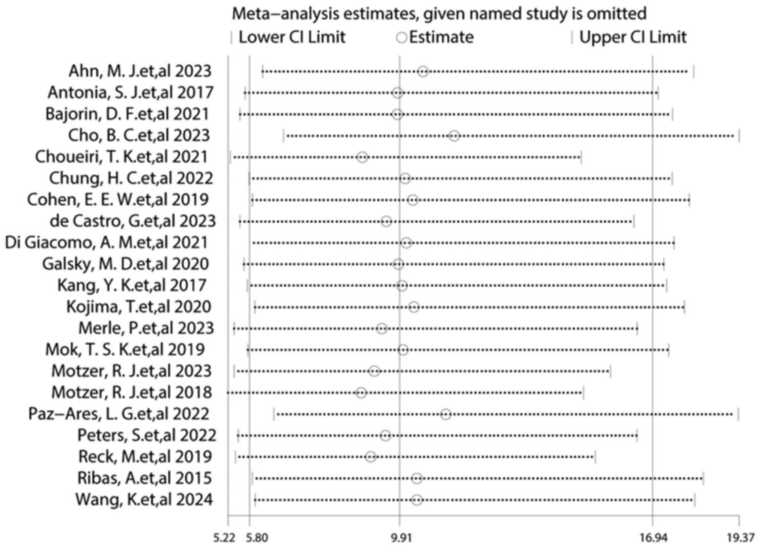

Figure 6. Sensitivity analysis (hyperthyroidism group).

tumor type, and prior endocrine history, which requires further investigation in future studies.

Moreover, blocking the PD-1 and PD-L1 pathways can induce varying degrees of thyroid inflammation in different individuals, resulting in hypothyroidism or hyperthyroidism. These findings suggest that distinct immune checkpoint blockade pathways affect the thyroid differently, likely due to differences in the degree of immune pathway activation and the specific targeting of thyroid cells. Lastly, thyroid dysfunction associated with ICIs may also be influenced by individual immune gene expression, tumor type, and prior endocrine history, which requires further investigation in future studies.

Limitations

Despite the representativeness and robustness of this meta-analysis, several limitations exist. Firstly, most included studies were single-center, which may have introduced selection bias into the sample and limited the generalizability of the findings. Secondly, the definition of thyroid dysfunction and diagnostic criteria varied across studies, which may have affected the estimation of the pooled effect. Additionally, although heterogeneity and subgroup analyses were conducted to control for the effects of different ICI types and tumor types, there may still have been uncontrolled confounders, such as patients' history of thyroid disease or family history. Thirdly, this study did not systematically collect data on the effects of different treatment cycles and doses on the risk of TD, nor did it explore the dose-response relationship. Fourth, the heterogeneity in the hypothyroidism-related analyses in this study reached 89.4%, and no clear source was identified even after systematic exploration. This may be related to the following objective factors: ① Missing data on potential confounding factors: The occurrence of hypothyroidism may be associated with patients' baseline immune status, concomitant medications (such as other drugs affecting thyroid function), etc., but these could not be included in the analysis due to insufficient data; ② Subtle differences unquantified at the study level: Some studies exhibited unreported variations in outcome severity grading, dose adjustment protocols, and follow-up monitoring frequency. These factors may collectively contribute to high heterogeneity; ③ True biological heterogeneity: The mechanism by which ICIs induce hypothyroidism may vary among individuals. Inherent differences in immune response intensity and thyroid tissue sensitivity across patients cannot be fully explained by the characteristics of existing studies. Furthermore, while publication bias was not significant in Egger's test, a possible influence of unpublished studies on the results cannot be entirely ruled out. Therefore, caution should be exercised when interpreting the results of this study, and prospective multicenter studies with large samples and rigorous designs are recommended to further validate the relationship between ICI treatment and TD.

Clinical significance

The findings of this meta-analysis hold significant value for clinical practice. Thyroid dysfunction is a frequent and notable adverse event in cancer patients undergoing ICI therapy, particularly when two ICIs are combined or when CTLA-4 inhibitors or PD-1 inhibitors are used alone. Clinicians should closely monitor patients' thyroid function during ICI treatment, especially in the early stages or for those receiving high doses. Regular monitoring of thyroid hormone levels and early detection of changes in thyroid

function enable timely interventions to prevent severe thyroid dysfunction. Moreover, the TD risk data provided in this study offer a foundation for developing personalized treatment plans. Clinicians can assess the risk of thyroid dysfunction based on factors such as the patient's tumor type, ICI selection, and medical history before treatment, and discuss potential side effects with patients to prepare for prevention. Ultimately, our discussion also emphasizes the dynamic evolution of ICI-related thyroid dysfunction and considers the limitations arising from heterogeneous follow-up periods and varying diagnostic definitions - areas that have been less systematically examined in previous meta-analyses. The clinical application of these findings could help optimize ICI treatment regimens, enhance patient safety and treatment adherence, and provide empirical support for managing endocrine adverse reactions associated with ICIs.

Conclusion

This systematic evaluation and meta-analysis identified a link between ICI treatment and the risk of developing thyroid dysfunction (TD) in oncology patients through a comprehensive analysis of 40 included studies. The use of ICIs increased the overall risk of thyroid dysfunction. Combination therapy further elevated this risk. ICI-associated hyperthyroidism was found to occur more frequently than hypothyroidism in the included studies. However, this finding appears to contrast with real-world clinical observations and previous literature, where hypothyroidism is generally more prevalent due to the evolution of transient hyperthyroidism into a permanent hypothyroid state. The discrepancy may reflect variations in follow-up duration, diagnostic criteria, and reporting practices across the included trials. These differences underscored the need for longitudinal follow-up to capture transient versus permanent thyroid status. Future studies should further investigate the biological mechanisms by which ICI treatment leads to TD, as well as the effects of factors such as dose and treatment cycle on the risk of TD, to provide a stronger scientific basis for optimizing and personalizing ICI treatment plans.

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Disclosure of conflict of interest

None.

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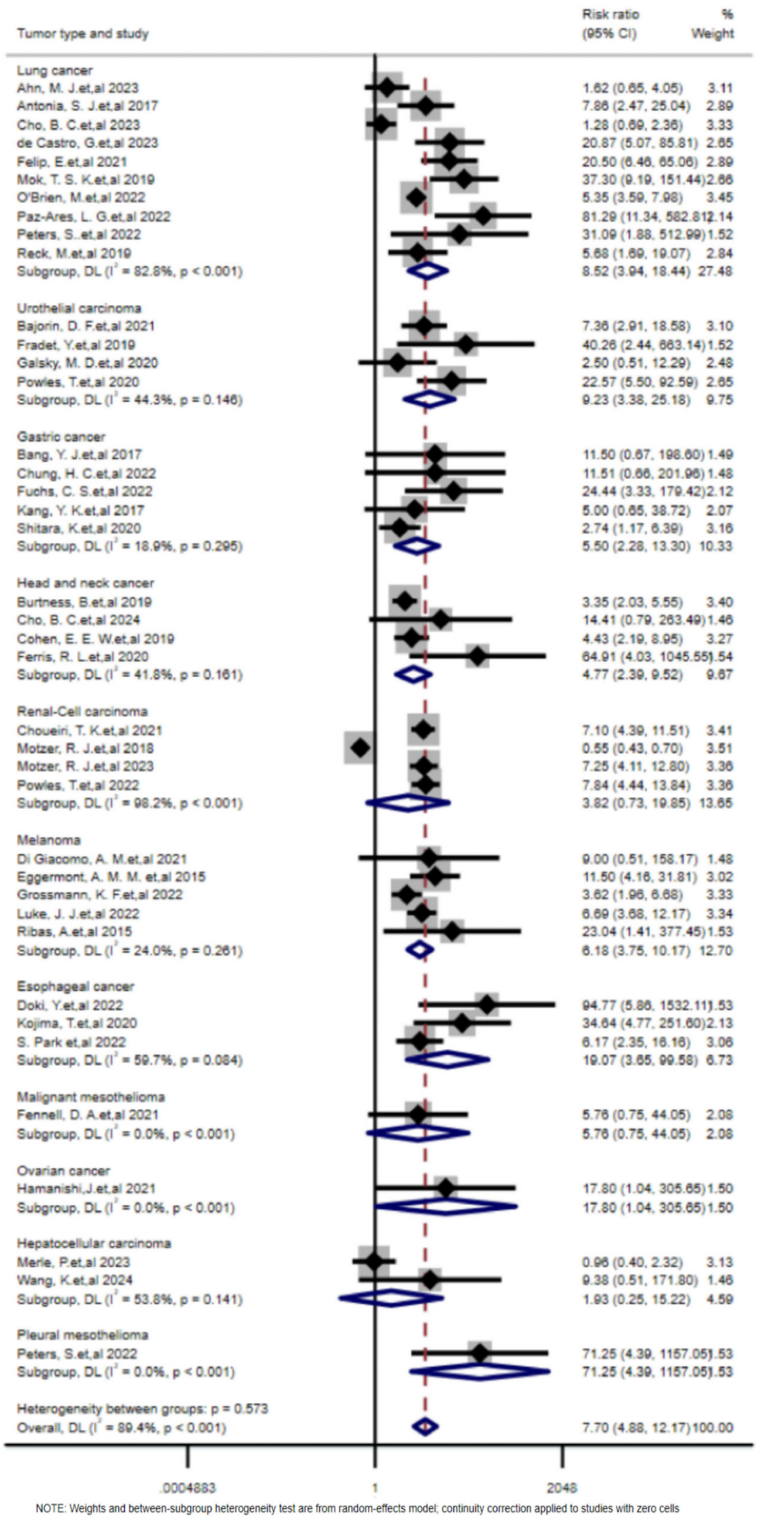
Supplementary Material. Search records

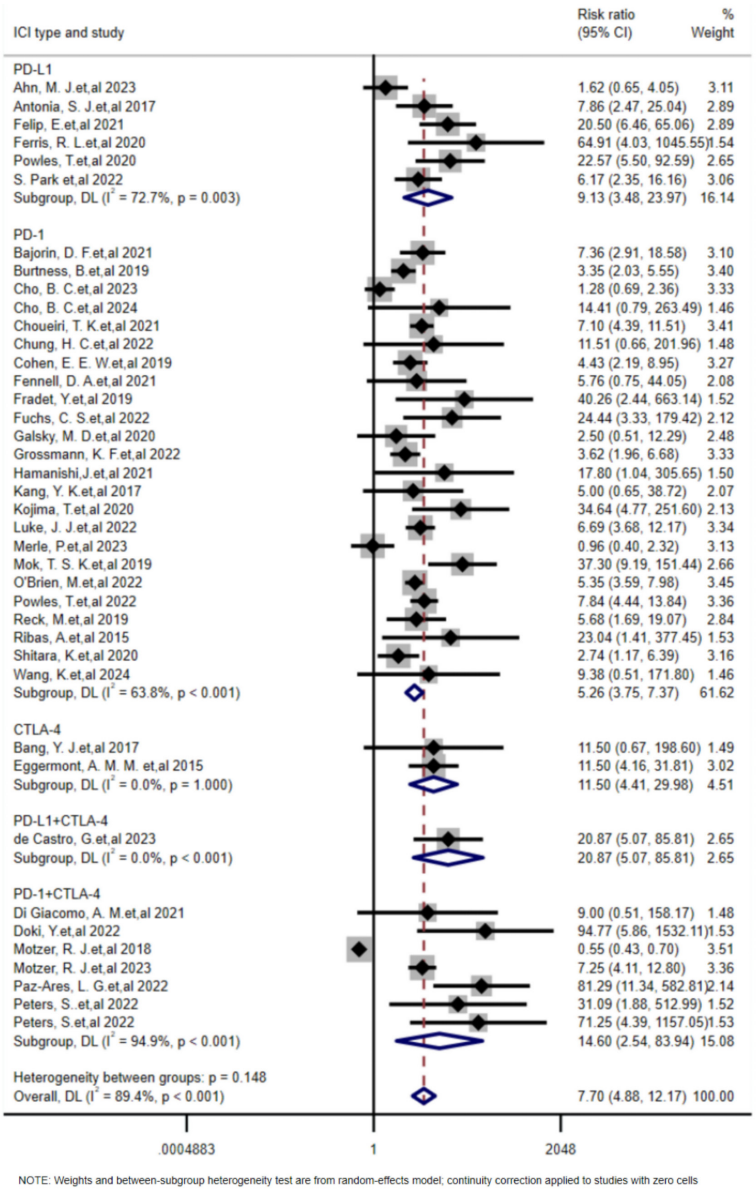
No.	Database	Search strategy	Results
1	PubMed	((((thyroid dysfunction[Text WORd]) OR ((“Thyroiditis”[Mesh]) OR (Thyroiditides[Text WORd]))) OR (((((Hyperthyroid[Text WORd]) OR (Hyperthyroids[Text WORd])) OR (Primary Hyperthyroidism[Text WORd])) OR (Hyperthyroidism, Primary[Text WORd])) OR (“Hyperthyroidism”[Mesh]))) OR ((“Hypothyroidism”[Mesh]) OR ((((((((((((((((((Hypothyroidisms[Text WORd]) OR (Thyroid-Stimulating HORmone Deficiency[Text WORd])) OR (Deficiency, Thyroid-Stimulating HORmone[Text WORd])) OR (HORmone Deficiency, Thyroid-Stimulating[Text WORd])) OR (Thyroid-Stimulating HORmone Deficiencies[Text WORd])) OR (Thyroid Stimulating HORmone Deficiency[Text WORd])) OR (TSH Deficiency[Text WORd])) OR (Deficiency, TSH[Text WORd])) OR (TSH Deficiencies[Text WORd])) OR (Secondary Hypothyroidism[Text WORd])) OR (Hypothyroidism, Secondary[Text WORd])) OR (Secondary Hypothyroidisms[Text WORd])) OR (Central Hypothyroidism[Text WORd])) OR (Central Hypothyroidisms[Text WORd])) OR (Hypothyroidism, Central[Text WORd])) OR (Primary Hypothyroidism[Text WORd])) OR (Hypothyroidism, Primary[Text WORd])) OR (Primary Hypothyroidisms[Text WORd]))))) AND ((((((((((((((((((TumORs[Title/Abstract]) OR (Neoplasia[Title/Abstract])) OR (Neoplasias[Title/Abstract])) OR (Neoplasm[Title/Abstract])) OR (TumOR[Title/Abstract])) OR (Cancer[Title/Abstract])) OR (Cancers[Title/Abstract])) OR (Malignant Neoplasm[Title/Abstract])) OR (Malignancy[Title/Abstract])) OR (Malignancies[Title/Abstract])) OR (Malignant Neoplasms[Title/Abstract])) OR (Neoplasm, Malignant[Title/Abstract])) OR (Neoplasms, Malignant[Title/Abstract])) OR (Benign Neoplasms[Title/Abstract])) OR (Neoplasms, Benign[Title/Abstract])) OR (Neoplasm, Benign[Title/Abstract])) OR (Benign Neoplasm[Title/Abstract])) OR (“Neoplasms”[Mesh])) AND ((((((((camrelizumab[Title/Abstract]) OR (Cemiplimab[Title/Abstract])) OR (Avelumab[Title/Abstract])) OR (pembrolizumab[Title/Abstract])) OR (durvalumab[Title/Abstract])) OR ((((((((((Anti-CTLA-4 MAb Ipilimumab[Title/Abstract]) OR (Anti CTLA 4 MAb Ipilimumab[Title/Abstract])) OR (Ipilimumab, Anti-CTLA-4 MAb[Title/Abstract])) OR (MDX 010[Title/Abstract])) OR (MDX-010[Title/Abstract])) OR (MDX010[Title/Abstract])) OR (MDX-CTLA-4[Title/Abstract])) OR (MDX CTLA 4[Title/Abstract])) OR (Yervoy[Title/Abstract])) OR (“Ipilimumab”[Mesh]))) OR ((((((((((MDX-1106[Title/Abstract]) OR (MDX1106[Title/Abstract])) OR (MDX 1106[Title/Abstract])) OR (Opdivo[Title/Abstract])) OR (BMS-936558[Title/Abstract])) OR (BMS936558[Title/Abstract])) OR (BMS 936558[Title/Abstract])) OR (ONO-4538[Title/Abstract])) OR (ONO4538[Title/Abstract])) OR (ONO 4538[Title/Abstract])) OR (“Nivolumab”[Mesh]))) OR ((“Immune Checkpoint InhibitORs”[Mesh]) OR ((((((((((((((((((((((((((((((((Checkpoint InhibitORs, Immune[Title/Abstract]) OR (Immune Checkpoint Blockers[Title/Abstract])) OR (Checkpoint Blockers, Immune[Title/Abstract])) OR (Immune Checkpoint InhibitOR[Title/Abstract])) OR (Checkpoint InhibitOR, Immune[Title/Abstract])) OR (CTLA-4 InhibitORs[Title/Abstract])) OR (CTLA 4 InhibitORs[Title/Abstract])) OR (Cytotoxic T-Lymphocyte-Associated Protein 4 InhibitORs[Title/Abstract])) OR (Cytotoxic T Lymphocyte Associated Protein 4 InhibitORs[Title/Abstract])) OR (Cytotoxic T-Lymphocyte-Associated Protein 4 InhibitOR[Title/Abstract])) OR (Cytotoxic T Lymphocyte Associated Protein 4 InhibitOR[Title/Abstract])) OR (CTLA-4 InhibitOR[Title/Abstract])) OR (CTLA 4 InhibitOR[Title/Abstract])) OR (PD-1 InhibitORs[Title/Abstract])) OR (PD 1 InhibitORs[Title/Abstract])) OR (Programmed Cell Death Protein 1 InhibitOR[Title/Abstract])) OR (Programmed Cell Death Protein 1 InhibitORs[Title/Abstract])) OR (PD-1 InhibitOR[Title/Abstract])) OR (InhibitOR, PD-1[Title/Abstract])) OR (PD 1 InhibitOR[Title/Abstract])) OR (Immune Checkpoint Blockade[Title/Abstract])) OR (Checkpoint Blockade, Immune[Title/Abstract])) OR (Immune Checkpoint Inhibition[Title/Abstract])) OR (Checkpoint Inhibition, Immune[Title/Abstract])) OR (PD-L1 InhibitORs[Title/Abstract])) OR (PD L1 InhibitORs[Title/Abstract])) OR (Programmed Death-Ligand 1 InhibitORs[Title/Abstract])) OR (Programmed Death Ligand 1 InhibitORs[Title/Abstract])) OR (PD-L1 InhibitOR[Title/Abstract])) OR (PD L1 InhibitOR[Title/Abstract])) OR (PD-1-PD-L1 Blockade[Title/Abstract])) OR (Blockade, PD-1-PD-L1[Title/Abstract])) OR (PD 1 PD L1 Blockade[Title/Abstract]))))) SORt by: Most Recent	359

2	Embase	#1 'TumORs':ab,ti OR 'Neoplasia':ab,ti OR 'Neoplasias':ab,ti OR 'Neoplasm':ab,ti OR 'TumOR':ab,ti OR 'Cancer':ab,ti OR 'Cancers':ab,ti OR 'Malignant Neoplasm':ab,ti OR 'Malignancy':ab,ti OR 'Malignancies':ab,ti OR 'Malignant Neoplasms':ab,ti OR 'Neoplasm, Malignant':ab,ti OR 'Neoplasms, Malignant':ab,ti OR 'Benign Neoplasms':ab,ti OR 'Neoplasms, Benign':ab,ti OR 'Neoplasm, Benign':ab,ti OR 'Benign Neoplasm':ab,ti #2 'Checkpoint InhibitORs,Immune':ab,ti OR 'Immune Checkpoint Blockers':ab,ti OR 'Checkpoint Blockers, Immune':ab,ti OR 'Immune Checkpoint InhibitOR':ab,ti OR 'Checkpoint InhibitOR, Immune':ab,ti OR 'CTLA-4 InhibitORs':ab,ti OR 'CTLA 4 InhibitORs':ab,ti OR 'Cytotoxic T-Lymphocyte-Associated Protein 4 InhibitORs':ab,ti OR 'Cytotoxic T Lymphocyte Associated Protein 4 InhibitORs':ab,ti OR 'Cytotoxic T-Lymphocyte-Associated Protein 4 InhibitOR':ab,ti OR 'Cytotoxic T Lymphocyte Associated Protein 4 InhibitOR':ab,ti OR 'CTLA-4 InhibitOR':ab,ti OR 'CTLA 4 InhibitOR':ab,ti OR 'PD-1 InhibitORs':ab,ti OR 'PD 1 InhibitORs':ab,ti OR 'Programmed Cell Death Protein 1 InhibitOR':ab,ti OR 'Programmed Cell Death Protein 1 InhibitORs':ab,ti OR 'PD-1 InhibitOR':ab,ti OR 'InhibitOR, PD-1':ab,ti OR 'PD 1 InhibitOR':ab,ti OR 'Immune Checkpoint Blockade':ab,ti OR 'Checkpoint Blockade, Immune':ab,ti OR 'Immune Checkpoint Inhibition':ab,ti OR 'Checkpoint Inhibition, Immune':ab,ti OR 'PD-L1 InhibitORs':ab,ti OR 'PD L1 InhibitORs':ab,ti OR 'Programmed Death-Ligand 1 InhibitORs':ab,ti OR 'Programmed Death Ligand 1 InhibitORs':ab,ti OR 'PD-L1 InhibitOR':ab,ti OR 'PD L1 InhibitOR':ab,ti OR 'PD-1-PD-L1 Blockade':ab,ti OR 'Blockade, PD-1-PD-L1':ab,ti OR 'PD 1 PD L1 Blockade':ab,ti #3 'MDX-1106':ab,ti OR 'MDX1106':ab,ti OR 'MDX 1106':ab,ti OR 'Opdivo':ab,ti OR 'BMS-936558':ab,ti OR 'BMS936558':ab,ti OR 'BMS 936558':ab,ti OR 'ONO-4538':ab,ti OR 'ONO4538':ab,ti OR 'ONO 4538':ab,ti #4 'SHR-1210':ab,ti OR 'SHR 1210':ab,ti OR 'carrelizumab':ab,ti #5 'Anti CTLA 4 MAb Ipilimumab':ab,ti OR 'Ipilimumab, Anti-CTLA-4 MAb':ab,ti OR 'MDX 010':ab,ti OR 'MDX-010':ab,ti OR 'MDX010':ab,ti OR 'MDX-CTLA-4':ab,ti OR 'MDX CTLA 4':ab,ti OR 'Yervoy':ab,ti #6 #2 OR #3 OR #4 OR #5 #7 'hypothyroidism'/exp OR 'hyperthyroidism'/exp #8 'randomized controlled trial':ab,ti OR 'randomized':ab,ti OR 'placebo':ab,ti #9 #1 AND #6 AND #7 AND #8	689

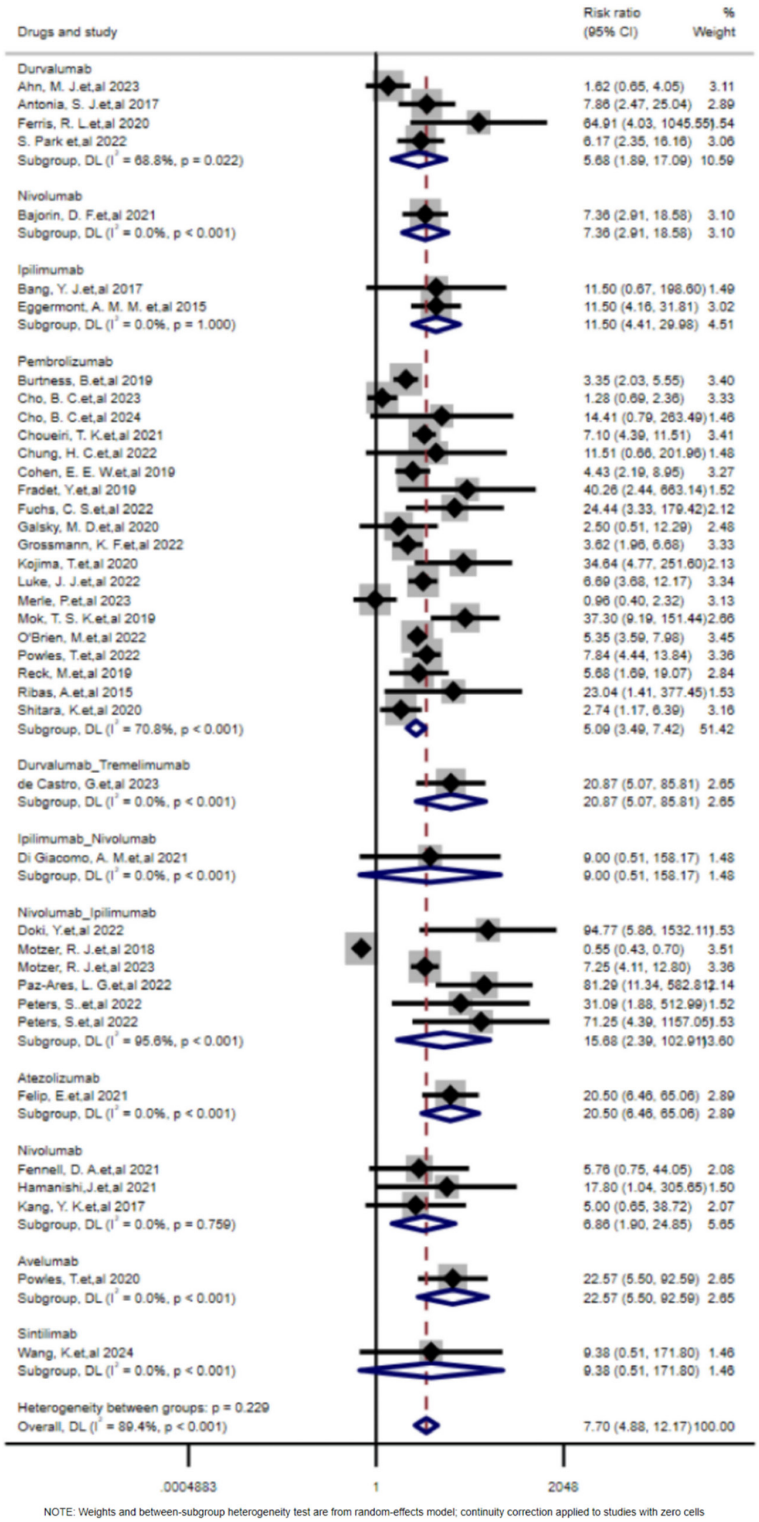
3	Cochrane Library	#1 MeSH descriptor: [Neoplasmsl] explode all trees OR (Tumors):ti,ab,kw OR (Neoplasial):ti,ab,kw OR (Neopasiasl):ti ab,kw OR (Neopasm):ti,ab,kw OR (Tumor):ti,ab,kw OR (Cancer):ti,ab,kw OR (Cancers):ti,ab,kw OR (Malignant Neoplasm):ti,ab,kw OR (Malignancy):ti,ab,kw OR (Malignancies):ti,ab,kw OR (Maligrant Neoplasms):ti,ab,kw OR (Neoplasm, Malignant):ti,ab,kw OR (Neoplasms. Malignant):ti ab,kw OR (Benign Neoplasmsl):ti,ab,kw OR (Neoplasms, Benignl):ti ab,kw OR (Neoplasm,Benign):ti ab kw OR (BenignNeoplasm):ti,ab,kw #2 MeSH descriptor: [Immune Checkpoint Inhibitors] explode all trees OR (Checkpoint Inhibitors, Immune):ti,ab,kw OR (Immune Checkpoint Blockers):ti,ab,kw OR (Checkpoint Blockers, Immune):ti,ab,kw OR (Immune Checkpoint Inhibitor):ti,ab,kw OR (Checkpoint Inhibitor, Immune):ti,ab,kw OR (CTLA-4 Inhibitors):ti,ab,kw OR (CTLA 4 Inhibitors):ti,ab,kw OR (Cytotoxic T-Lymphocyte-Associated Protein 4 Inhibitors):ti,ab,kw OR (Cytotoxic T Lymphocyte Associated Protein 4 Inhibitors):ti,ab,kw OR (Cytotoxic T-Lymphocyte-Associated Protein 4 Inhibitor):ti,ab,kw OR (Cytotoxic T Lymphocyte Associated Protein 4 Inhibitor):ti,ab,kw OR (CTLA-4 Inhibitor):ti,ab,kw OR (CTLA 4 Inhibitor):ti,ab,kw OR (PD-1 Inhibitors):ti,ab,kw OR (PD 1 Inhibitors):ti,ab,kw OR (Programmed Cell Death Protein 1 Inhibitor):ti,ab,kw OR (Programmed Cell Death Protein 1 Inhibitors):ti,ab,kw OR (PD-1 Inhibitor):ti,ab,kw OR (Inhibitor, PD-1):ti,ab,kw OR (PD 1 Inhibitor):ti,ab,kw OR (Immune Checkpoint Blockade):ti,ab,kw OR (Checkpoint Blockade, Immune):ti,ab,kw OR (Immune Checkpoint Inhibition):ti,ab,kw OR (Checkpoint Inhibition, Immune):ti,ab,kw OR (PD-L1 Inhibitors):ti,ab,kw OR (PD L1 Inhibitors):ti,ab,kw OR (Programmed Death-Ligand 1 Inhibitors):ti,ab,kw OR (Programmed Death Ligand 1 Inhibitors):ti,ab,kw OR (PD-L1 Inhibitor):ti,ab,kw OR (PD L1 Inhibitor):ti,ab,kw OR (PD 1 PD L1 Blockade):ti,ab,kw #3 MeSH descriptor: [Ipilimumab] explode all trees (Anti-CTLA-4 MAb Ipilimumab): ti, ab,kw OR (Anti CTLA 4 MAb Ipilimumab): ti, ab,kw OR (Ipilimumab, Anti-CTLA-4 MAb): ti, ab,kw OR (MDX 010): ti, ab,kw OR (MDX-010): ti, ab,kw OR (MDX010): ti, ab,kw OR (MDX-CTLA-4): ti, ab,kw OR (MDX CTLA 4): ti, ab,kw OR (Yervoy): ti, ab,kw #4 MeSH descriptor: [Nivolumab] explode all trees OR (MDX-1106):ti,ab,kw OR (MDX1106):ti,ab,kw OR (MDX 1106):ti,ab,kw OR (Opdivo):ti,ab,kw OR (BMS-936558):ti,ab,kw OR (BMS936558):ti,ab,kw OR (BMS 936558):ti,ab,kw OR (ONO-4538):ti,ab,kw OR (ONO4538):ti,ab,kw OR (ONO 4538):ti,ab,kw #5 (SHR-1210):ti,ab,kw OR (SHR 1210):ti,ab,kw OR (carrelizumab):ti,ab,kw OR (atezolizumab):ti,ab,kw OR (avelumab):ti,ab,kw OR (pembrolizumab):ti,ab,kw OR (durvalumab):ti,ab,kw #6 #2 OR #3 OR #4 OR #5 #7 MeSH descriptor: [Hypothyroidism] explode all trees OR (Hypothyroidisms): ti, ab,kw OR (Thyroid-Stimulating Hormone Deficiency): ti, ab,kw OR (Deficiency, Thyroid-Stimulating Hormone): ti, ab,kw OR (Hormone Deficiency, Thyroid-Stimulating): ti, ab,kw OR (Thyroid-Stimulating Hormone Deficiencies): ti, ab,kw OR (Thyroid Stimulating Hormone Deficiency): ti, ab,kw OR (TSH Deficiency): ti, ab,kw OR (Deficiency, TSH): ti, ab,kw OR (TSH Deficiencies): ti, ab,kw OR (Secondary Hypothyroidism): ti, ab,kw OR (Hypothyroidism, Secondary): ti, ab,kw OR (Secondary Hypothyroidisms): ti, ab,kw OR (Central Hypothyroidism): ti, ab,kw OR (Central Hypothyroidisms): ti, ab,kw OR (Hypothyroidism, Central): ti, ab,kw OR (Primary Hypothyroidism): ti, ab,kw OR (Hypothyroidism, Primary): ti, ab,kw OR (Primary Hypothyroidisms): ti, ab,kw #8 MeSH descriptor: [Hyperthyroidism] explode all trees OR (Hyperthyroid) OR (Hyperthyroids) OR (Primary Hyperthyroidism) OR (Hyperthyroidism, Primary) #9 MeSH descriptor: [Thyroiditis] in all MeSH products OR (thyroid dysfunction) #10 #7 OR #8 OR #9 #11 #1 AND #6 AND #10	288



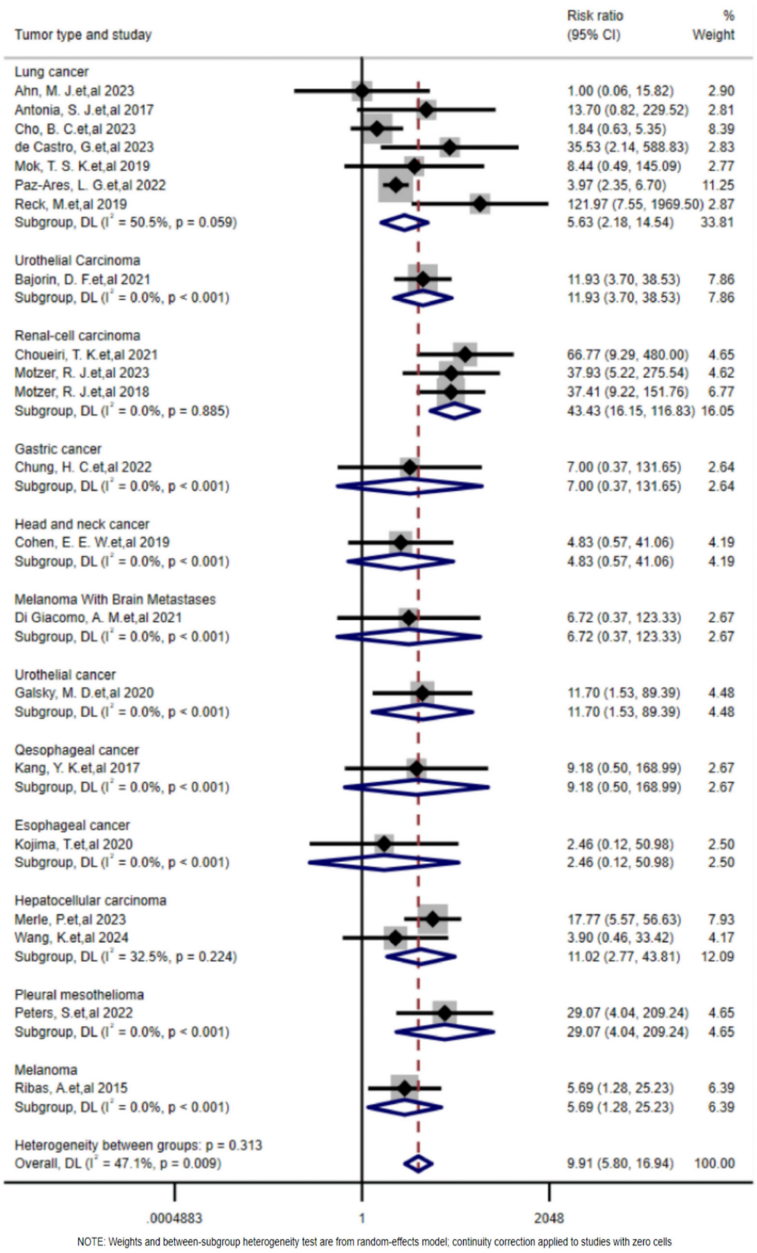
Supplementary Figure 1. Subgroup analysis of tumor types (hypothyroidism group).



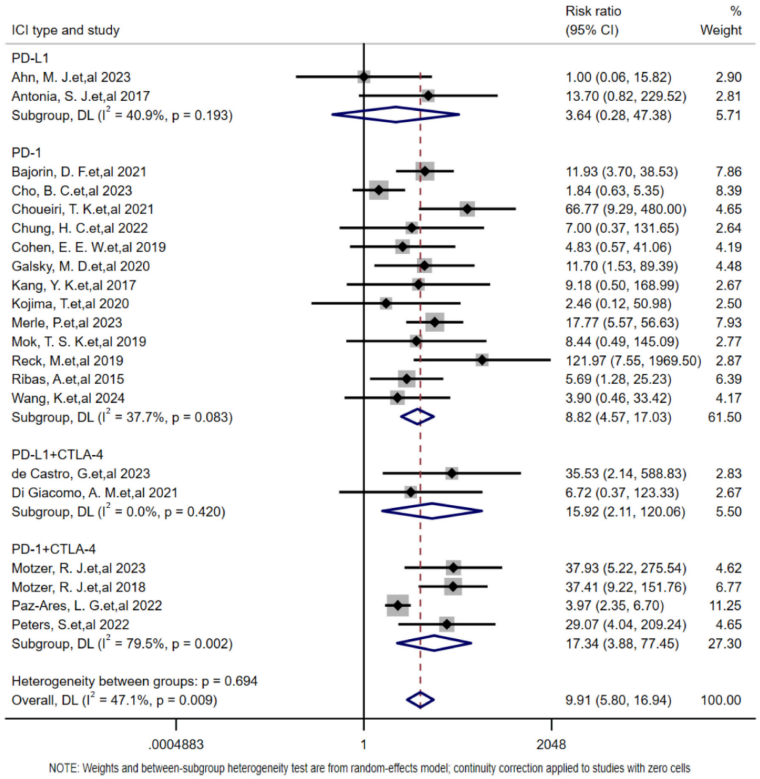
Supplementary Figure 2. Subgroup analysis of ICI types (hypothyroidism group).



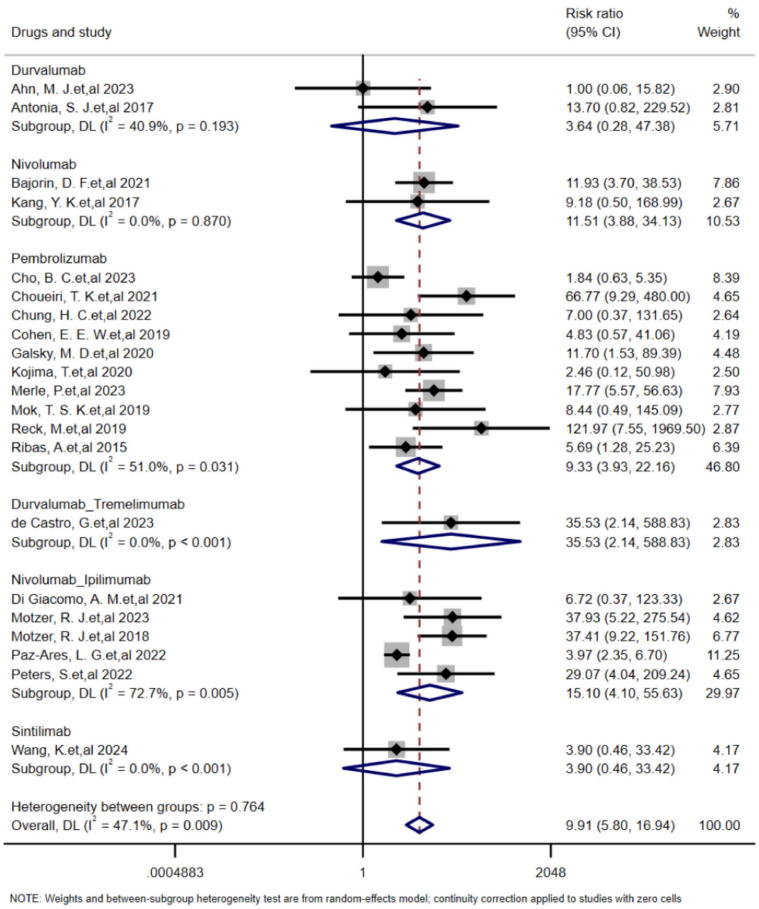
Supplementary Figure 3. Subgroup analysis of drug classes (hypothyroidism group).



Supplementary Figure 4. Subgroup analysis of tumor types (hyperthyroidism group).



Supplementary Figure 5. Subgroup analysis of ICI types (hyperthyroidism group).



Supplementary Figure 6. Subgroup analysis of drug classification (hyperthyroidism group).