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Original Article

Immune Checkpoint Inhibitor-related New-onset Thyroid Dysfunction: A Retrospective Analysis Using the US FDA Adverse Event Reporting System

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Abstract

Objectives: The study aimed to investigate the prevalence and demographic characteristics of an immune checkpoint inhibitor (ICI)-related thyroid dysfunction (ICI-TD), and to explore risk factors of poor clinical outcome using data from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).

Methods: This is a retrospective study. All cases, aged over 18-year olds, of new-onset or new-diagnosed thyroid dysfunction related to FDA-approved ICIs from January 1, 2011 to December 31, 2020 were identified using FAERS. Data of age, gender, other combined endocrinopathies related to ICIs besides ICI-TDs, and the prognosis was analyzed.

Results: In total, 2.60% (2971/114 121) cases of ICI-TDs were identified. Among them, 1842 (62.0%) developed hypothyroidism, 675 (22.7%) were hyperthyroidism, and 454 (15.3%) presented in thyroiditis without the mention of thyroid function. Patients on anti- programmed cell death protein-1 (PD-1) therapy displayed higher risk of hypothyroidism compared with other 3 regimens, respectively ($P < .01$ for all). The likelihood of other immune-related endocrinopathies in patients on the combination therapy of anti-cytotoxic T-cell-associated protein-4 (CTLA-4) and anti-PD-1 was significantly elevated than anti-PD-1 (odds ratio [OR] 2.362, 95% confidence interval [CI] [1.925-2.898], $P < .001$) and anti-programmed death-ligand 1 (PD-L1) regimens (OR 4.857, 95%CI [3.228-7.308], $P < .001$). The risk of severe cases was positively related to hypothyroidism in individuals on anti-PD-1 therapy (OR 1.587, 95%CI [1.146-2.197], $P = .005$) and those on anti-CTLA-4 therapy (OR 3.616, 95%CI [1.285-10.171], $P = .015$). The risk of severe cases was positively associated with the comorbidity with other endocrinopathies (anti-PD-1 group, OR 0.285, 95%CI [0.200-0.467], $P < .001$; anti-PD-1+anti-CTLA-4 group, OR 0.574, 95%CI [0.371-0.890], $P = .013$).

Conclusions: Regular monitor of thyroid function is indispensable, since ICI-TDs manifested as hypothyroidism or hyperthyroidism, especially those on the combination therapy. Awareness among health care professionals is critical when hypothyroidism occurs, which might indicate poor clinical outcomes.

Key words: immune checkpoint inhibitors; immune-related adverse event; thyroid dysfunction; thyroiditis; prognosis.

Implications for Practice

ICI-associated thyroid dysfunction (ICI-TDs) is a leading subtype of endocrine-associated immune-related adverse events (irAEs). The current study is a retrospective study on new-onset ICI-TDs according to real-world data from the US FDA Adverse Event Reporting System (FAERS). Our study revealed that the incidence of ICI-TDs was 2.60%. Thyrotoxic crisis was reported in 11/2971 patients with ICI-TDs. Our study indicated that patients on anti-PD-1 therapy displayed a higher risk of hypothyroidism compared with patients on PD-L1 inhibitors, CTLA-4 inhibitors, or the combination therapy of PD-1+CTLA-4 inhibitors. Patients on the combination therapy of anti-CTLA-4 and anti-PD-1 showed the highest of other immune-related endocrinopathies compared with other mono-therapy. The development of hypothyroidism and elder age was related to hospitalization, to be life-threatened and death. We also discovered that the co-occurrence of other endocrinologic irAEs was associated with a higher risk of death.

Introduction

Since the past several years, immune checkpoint inhibitors (ICIs), including programmed cell death protein-1 (PD-1) inhibitors, programmed death-ligand 1 (PD-L1) inhibitors, and cytotoxic T-cell-associated protein-4 (CTLA-4) inhibitors, have emerged as a remarkable therapeutic improvement for cancer patients of advanced stage. After the approval of ICIs for the treatment of a broad subtype of

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malignancies from the US Food and Drug Administration (FDA), immune-related adverse events (irAEs) of ICIs, including endocrinopathies, were recognized in a proportion of patients receiving ICI therapy.[1] Common types of ICI-related endocrinopathies are thyroid dysfunction, hypophysitis, primary adrenal insufficiency (PAI), and type 1 diabetes mellitus (DM).[2]

As a leading subtype of endocrine-related irAEs, ICI-related thyroid dysfunction (ICI-TDs) could present as overt or subclinical hypothyroidism, hyperthyroidism, and/or thyroiditis. However, the incidence of hypothyroidism or hyperthyroidism varied among statistics from randomized clinical trials (RCTs) of different ICIs and meta-analyses.[3-5] Given the increasing application of ICI therapy in clinical practice and possible life-threatening results caused by thyrotoxic crisis and myxedema coma, it is critical to obtain accurate and comprehensive data from a large population of the incidence, clinical manifestations, and prognosis of ICI-related thyroid dysfunction. Therefore, we carried on a retrospective study to investigate the prevalence and demographic characteristics of ICI-related thyroid dysfunction and to explore risk factors of poor clinical outcome using data from the US FDA Adverse Event Reporting System (FAERS).

Methods

Settings

This is a retrospective study based on the FAERS database. The FAERS is a pharmacovigilance database for adverse events associated with FDA-approved medications. All cases, aged over 18-year olds, of new-onset or new-diagnosed thyroid dysfunction related to FDA-approved ICIs from 1st January 2011 to 31st December 2020 were identified using FAERS. Only 6 under-age patients with ICIs-related thyroid dysfunction were reported, who was not involved in the statistical analysis due to the small reported number and distinguishing characteristics between adolescents and adults.

There were 7 ICIs approved by FDA due to December 31, 2020, which were all involved in this study. The 7 ICIs were anti-CTLA-4 mono-antibody (ipilimumab), anti-PD-1 mono-antibodies (nivolumab, pembrolizumab, and cemiplimab), and anti-PD-L1 mono-antibodies (atezolizumab, avelumab, and durvalumab). New-onset hypothyroidism, hyperthyroidism, or thyroiditis in patients receiving ICI therapy was considered the diagnosis of ICI-TDs. The definition of hypothyroidism included the following FAERS terms as an adverse reaction: hypothyroidism, autoimmune hypothyroidism, immune-mediated hypothyroidism, and primary hypothyroidism. The definition of hyperthyroidism included the following FAERS terms: hyperthyroidism, autoimmune hyperthyroidism, immune-mediated hyperthyroidism, and primary hyperthyroidism. The definition of thyroiditis included the following FAERS terms: thyroiditis, autoimmune thyroiditis, immune-mediated thyroiditis, and autoimmune thyroid disorder.

The hypothyroidism subgroup included patients diagnosed with hypothyroidism, hypothyroidism accompanied with thyroiditis, and hypothyroidism induced by destructive thyroiditis (manifested as transient hyperthyroidism followed by hypothyroidism). When one case was diagnosed with hyperthyroidism, hypothyroidism, and thyroiditis at the same time, which was reckoned as the manifestation of ICIs-related destructive thyroiditis, these patients were assigned to the hypothyroidism subgroup. The hyperthyroidism subgroup included patients diagnosed with hyperthyroidism and hyperthyroidism accompanied with thyroiditis. Thyroiditis referred to those diagnosed as thyroiditis without thyroid function information.

Patients with secondary or pituitary hypothyroidism after ICIs treatment were excluded. Also, we accumulated data of other combined endocrinopathies related to ICIs besides ICI-TDs and prognosis. Situations of hospitalization, disabled, life-threatened, and death were considered as severe cases. Because all data analyzed in this study were available in public resource and all cases were anonymous, the study was exempt from informed consent and ethics.

Statistics

Quantitative variables in accordance with normal distribution were analyzed using 1-way ANOVA test among multiple groups. As qualitative variables, the proportion of ICI-TDs with total ICIs-related adverse events during the same study period or population were compared using χ^2 test by sex categories, age, and reporting year. Comparisons between each treatment regimens were performed using the Bonferroni adjustment method. We used logistic regression analysis to evaluate the association between treatment regimen and risk of ICI-TDs. Statistical analysis was performed using SPSS 17.0 (IBM, USA). $P < .05$ was considered statistical significant.

Results

Incidences of ICI-TDs in All Cases With Adverse Events

A total of 2971 cases of ICI-TDs were identified in 114 121 patients reported as adverse events related to ICIs, and the incidence of ICI-TDs was 2.60%. Among them, 1842 patients (62.0%) developed hypothyroidism, 675 (22.7%) were hyperthyroidism, and 454 (15.3%) presented with thyroiditis. Among patients with hypothyroidism, 171 (9.3% of 1842) cases manifested with destructive thyroiditis, which presented with hyperthyroidism along with hypothyroidism. Thyrotoxic crisis was reported in 11 patients, 5 of them received anti-PD-1 therapy (nivolumab) along and 6 on the combination therapy of anti-PD-1 + anti-CTLA-4 (nivolumab-ipilimumab treatment). There was no reported case of ICIs-induced myxedema coma.

Subtypes of Different Regimens in Patients With ICIs-TDs

In all patients with ICI-TDs who received anti-PD-1 therapy, 59.3% (1060 of 1787) of them were treated with nivolumab, 40.6% (725 of 1787) were on pembrolizumab, and 0.1% (2 of 1787) were on cemiplimab. Among patients with ICI-TDs on PD-L1 inhibitors, 65.0% (219 of 337) of them were on atezolizumab, 5.6% (19 of 337) were on avelumab, and 29.4% (99 of 337) were on durvalumab. There was only one kind of CTLA-4 inhibitor (ipilimumab). In ICI-TDs patients receiving the combination therapy of anti-CTLA-4 and anti-PD-1, 92.4% (617 of 668) of them were on nivolumab-ipilimumab treatment and 7.6% (51 of 668) were on pembrolizumab-ipilimumab therapy.

Subtypes of ICIs-TDs in Patients With Different Regimens

In the 3 subtypes of ICIs-TDs, there was a higher risk of hypothyroidism compared with hyperthyroidism or thyroiditis in patients on ICIs therapy (χ^2 = 194.10, P < .001). Patients on anti-PD-1 therapy displayed higher risk of hypothyroidism compared with other 3 regimens, respectively (anti-PD-L1, χ^2 = 9.56, P = .002; anti-CTLA-4, χ^2 = 188.56, P < .001; anti-PD-1+anti-CTLA-4, χ^2 = 16.61, P < .001). There were no significant differences in the other 3 regimen groups in thyroid function distribution, nor in the 3 different kinds of PD-1 inhibitors or PD-L1 inhibitors.

Demographic Characteristics of ICIs-TDs

In all patients with ICI-TDs, 1584 case individuals (53.3%) were male, 1171 (39.4%) were female, and 216 subjects (7.3%) were not specified. The incidence of ICI-TDs was calculated as ICI-TDs cases divided by all reported cases with adverse events of male or female sex category. Female individuals showed higher risk of ICI-TDs compared with the incidence in male patients, and significant differences was observed in the incidence of ICI-TDs by sex categories in all cases and those receiving anti-PD-1 therapy, anti-PD-L1 therapy, and the combination of anti-PD-1 + anti-CTLA-4 therapy, respectively (all regimen cases, male vs female, 1584/62 594 [2.5%] vs 1171/38 179 [3.1%], χ^2 = 25.67, P < .001; anti-PD-1 therapy, 957/41 282 [2.3%] vs 683/24 673 [2.8%], χ^2 = 12.90, P < .001; anti-PD-L1 therapy, 157/8522 [1.8%] vs 156/6099 [2.6%], χ^2 = 8.69, P = .003; anti-CTLA-4 therapy, 102/12 790 [0.8%] vs 67/7407 [0.9%], χ^2 = 0.65, P = .421; anti-PD-1+ anti-CTLA-4 therapy, 368/12 790 [2.9%] vs 265/7407 [3.5%], χ^2 = 7.58, P = .006).

Of all 2971 cases, 1189 (40.0%) were at 18-64 years of age, 1291 (43.5%) were over 65-year olds, and 490 (16.5%) were not specified of age. For the age distribution in ICI-TDs patients, no significant difference was discovered in ICPs-TDs between younger patients (age < 65 years, 1189/36 672 [3.2%]) comparing with those elder than 65-year olds (1291/41 679 [3.1%], χ^2 = 1.33, P = .248). Similar results between different age groups were observed in patients receiving anti-PD-1 therapy (<65 vs ≥65, 2.8% [623/22 423] vs 3.0% [820/27 546], χ^2 = 1.74, P = .188), anti-CTLA-4 therapy (<65 vs ≥65, 1.1% [90/8456] vs 0.8% [60/7194], χ^2 = 2.17, P = .141), and the combined therapy of anti-PD-1 + anti-CTLA-4 (<65 vs ≥65, 3.8% [321/8456] vs 3.9% [279/7194], χ^2 = 0.071, P = .790). However, patients less than 65-year olds showed a higher risk of ICI-TDs on anti-PD-L1 therapy comparing with those elder than 65-year olds (<65 vs ≥65, 2.7% [155/5793] vs 1.9% [132/6939], χ^2 = 8.57, P = .003). As for thyroid function, patients aged less than 65 years were more likely to develop hyperthyroidism instead of hypothyroidism compared with those elder than 65-year olds (OR = 1.083, 95% confidence interval [CI]: 1.022-1.147, χ^2 = 7.35, P = .007). The predisposition of hyperthyroidism in younger aged patients remained significant in individuals on anti-PD-1 + anti-CTLA-4 therapy (OR = 1.245, 95%CI: 1.079-1.437, χ^2 = 9.19, P = .002), but the significance disappeared in subgroups of different ICIs mono-therapy (anti-PD-1, χ^2 = 3.897, P = .143; anti-PD-L1, χ^2 = 2.102, P = .350; anti-CTLA-4, χ^2 = 0.802, P = .670).

The Cancer Type in Patients With ICI-TDs

In all patients with ICI-TDs, 12.9% (385 of 2971) of them were with renal cell carcinoma, 31.8% (944 of 2971) were with non-small cell lung carcinoma (NSCLC), 31.1% (923 of 2971) were with melanoma, and 24.2% (719 of 2971) were with other types of cancer including squamous-cell carcinoma (Table 1).

The Co-occurrence of Other Endocrinopathies in Patients With ICIs-TDs

Patients with ICI-TDs developed other immune-related endocrinopathies including hypophysitis, type 1 diabetes, and adrenal insufficiency, were considered the situation of co-occurrence of other endocrinopathies. The likelihood of other immune-related endocrinopathies in patients on the combination therapy of anti-CTLA-4 + anti-PD-1 was significantly elevated than anti-PD-1 and anti-PD-L1 regimens (anti-PD-1, OR 2.362, 95%CI [1.925-2.898], P < .001; anti-PD-L1, OR 4.857, 95%CI [3.228-7.308], P < .001).

Distribution of ICIs-TDs Based on Reporting Year

Overall, a consistent increasing trend was observed in cases reported as ICI-TDs, from 182 in 2015 and before to 913 in 2020 (Table 1). The proportion of ICI-TDs to all reported ICIs related adverse events significantly increased from 1.8% (182-10 052) in 2015 and before, to 3.0% (913-30 246) in 2020 (χ^2 = 59.79, P < .001, Bonferroni corrected). In anti-PD-1 therapy subgroup, the incidence of thyroid disorder significantly raised from 1.8% (67-3788) in 2015 to 2.5% (483-19 254) in 2020 (χ^2 = 7.436, P = .006, Bonferroni corrected). The incidence of thyroid dysfunction in subjects on anti-PD-L1 therapy was remarkably increased over time, from 1.6% (6-376) in 2016 to 2.7% (169-6221 in 2020; χ^2 = 22.21, P = .001, Bonferroni corrected). The reported number of ICI-TDs in patients on anti-CTLA-4 mono-therapy declined over time, from 1.6% (89-6200) in 2015 and before to 0.1% (6-4771) in 2020 (χ^2 = 108.25, P < .001, Bonferroni corrected). A significant increase was discovered in incidence of thyroid diseases in individuals receiving the combined regimen of anti-PD-1 + anti-CTLA-4 therapy, from 0.4% (26-6200) in 2015 and before to 5.3% 255-4771) in 2020 (χ^2 = 262.97, P < .001, Bonferroni corrected).

Clinical Outcomes in Patients With ICIs-TDs

In terms of prognosis of 2971 patients with ICIs-TDs, 1747 (58.8%) cases were severe. Among the severe cases, 1065 (61.0%) were hospitalized, 247 (14.1%) were life-threatened or disabled, and there were 435 (24.9%) cases of death due to various causes. Patients on the combination therapy of anti-PD-1 + anti-CTLA-4 indicated higher risk of severe cases comparing with those on anti-PD-1 therapy (χ^2 = 58.36, P < .001), anti-PD-L1 therapy (χ^2 = 30.32, P < .001), or anti-CTLA-4 therapy (χ^2 = 18.24, P < .001). No significant difference was found in the risk of severe cases in individuals on anti-PD-1 therapy, anti-PD-L1 therapy, or anti-CTLA-4 therapy (χ^2 = 0.019, P = .890). Patients on anti-PD-1 therapy had higher risk of death, which was resulted from all possible causes as reported in FAERS, including advanced malignancy, comparing with other regimens (anti-PD-L1, χ^2 = 16.02, P < .001; anti-CTLA-4, χ^2 = 5.12, P = .023; anti-PD-1+anti-CTLA-4, χ^2 = 6.87, P = .009). The combination therapy of anti-PD-1 + anti-CTLA-4 suggested no significant influence

Table 1. Clinical characteristics of patients with ICI-related thyroid disorders.

Characteristics	All (*n* = 2971)	Anti-PD-1 therapy (*n* = 1787)	Anti-PD-L1 therapy (*n* = 337)	Anti-CTLA-4 therapy (*n* = 179)	Anti-PD-1 and anti-CTLA-4 therapy (*n* = 668)
Sex categories					
Male (*n*, %)[a]	1584 (53.3)	957 (53.6)	157 (46.6)	102 (57.0)	368 (55.1)
Female (*n*, %)	1171 (39.4)	683 (38.2)	156 (46.3)	67 (37.4)	265 (39.7)
Not specified (*n*, %)	216 (7.3)	147 (8.2)	24 (7.1)	10 (5.6)	35 (5.2)
Age (years)					
18-64 (*n*, %)	1189 (40.0)	623 (34.9)	155 (46.0)	90 (50.3)	321 (48.1)
≥65 (*n*, %)	1291 (43.5)	820 (45.9)	132 (39.2)	60 (33.5)	279 (41.8)
Not specified (*n*, %)	490 (16.5)	344 (19.2)	50 (14.8)	29 (16.2)	68 (10.1)
Reporting year					
2015 and before (*n*, %)	182 (6.1)	67 (3.4)	0 (0)	89 (49.7)	26 (3.9)
2016 (*n*, %)	229 (7.7)	153 (8.6)	6 (1.8)	32 (17.9)	38 (5.7)
2017 (*n*, %)	385 (13.0)	255 (14.3)	24 (7.1)	27 (15.1)	79 (11.8)
2018 (*n*, %)	588 (19.8)	400 (22.4)	53 (15.7)	15 (8.4)	120 (18.0)
2019 (*n*, %)	674 (22.7)	429 (24.0)	85 (25.2)	10 (5.6)	150 (22.5)
2020 (*n*, %)	913 (30.7)	483 (27.0)	169 (50.1)	6 (3.4)	255 (38.2)
Cancer types (*n*, %)					
Renal cell carcinoma	385 (12.9)	226 (12.7)	18 (5.3)	0 (0.0)	141 (21.2)
Non-small cell lung carcinoma	944 (31.8)	729 (40.8)	166 (49.3)	2 (1.1)	47 (7.0)
Melanoma	923 (31.1)	376 (21.0)	10 (3.0)	144 (80.4)	393 (58.8)
Other types	719 (24.2)	456 (25.5)	143 (42.4)	33 (18.5)	87 (13.0)
Thyroid dysfunction types (*n*, %)					
Hypothyroidism	1842 (62.0)	1188 (66.5)	209 (62.0)	99 (55.3)	346 (51.8)
Hyperthyroidism	675 (22.7)	362 (20.2)	97 (28.8)	50 (27.9)	166 (24.8)
Thyroiditis	454 (15.3)	237 (13.3)	31 (9.2)	30 (16.8)	156 (23.4)
Prognosis (*n*, %)					
Hospitalized	1065 (35.8)	527 (29.5)	126 (37.4)	71 (39.7)	341 (51.0)
Life-threatened or disabled	247 (8.3)	160 (9.0)	19 (5.6)	10 (5.6)	58 (8.7)
Death	435 (14.6)	296 (16.6)	39 (11.6)	18 (10.1)	82 (12.3)
Accompanied with other endocrinologic irAEs (*n*, %)	616 (20.7)	299 (16.7)	30 (8.9)	72 (40.2)	215 (32.2)

[a]% referred to the proportion of age, gender, reporting year, thyroid dysfunction type, prognosis or other immune related endocrinopathies with all ICI-TDs cases in different treatment regimens.
Abbreviation: irAE, immune-related adverse event.

on the risk of death comparing with anti-PD-L1 therapy (χ^2 = 0.104, *P* = .747) or anti-CTLA-4 therapy (χ^2 = 0.668, *P* = .414).

In the subgroup of patients on PD-1 inhibitors, nivolumab treatment showed a positive correlation with the risk of death (OR 1.355, 95%CI [1.019-1.803], *P* = .037] and severe clinical outcomes (OR 1.687, 95%CI [1.343-2.120], *P* < .001). In the combination therapy subgroup, nivolumab+ ipilimumab therapy indicated a higher risk of severe cases (OR 4.506, 95%CI [2.320-8.752], *P* < 0.001). No difference was found in patients on the 3 medications of PD-L1 inhibitors.

Further analysis was conducted to explore confounders of prognosis, including age, sex categories, cancer types, thyroid function, and the co-occurrence of other immune-related endocrinopathies, in patients on different regimens. In patients on the combination therapy of anti-PD-1+anti-CTLA-4, the risk of death was positively associated with the cancer type of melanoma (OR 2.674, 95%CI [1.010-7.080], *P* = .048), while NSCLC and renal cell carcinoma showed no significance in prognosis. On the aspect of thyroid function, the risk of severe cases in individuals on anti-PD-1 therapy increased 58.7% when they developed hypothyroidism (OR 1.587, 95%CI [1.146-2.197], *P* = .005). The risk of severe cases in individuals on anti-CTLA-4 therapy increased 261.6% when they developed hypothyroidism (OR 3.616, 95%CI [1.285-10.171], *P* = .015], and was also positively associated with hyperthyroidism (OR 3.460, 95%CI [1.143-10.473], *P* = .028). The risk of severe cases was inversely associated with none comorbidity with other endocrinopathies in patients on anti-PD-1 therapy, anti-PD-L1 therapy and the combination therapy of anti-PD-1+anti-CTLA-4 (anti-PD-1, OR 0.285, 95%CI [0.200-0.467], *P* < .001; anti-PD-L1, OR 0.234, 95%CI [0.064-0.862], *P* = .029; anti-PD-1+anti-CTLA-4, OR 0.574, 95%CI [0.371-0.890], *P* = .013). On the opposite, the risk of death was positively associated with none comorbidity with other endocrinopathies in patients on anti-PD-1 therapy and the combination therapy of anti-PD-1+anti-CTLA-4 (anti-PD-1, OR 1.733, 95%CI [1.153-2.606],

P = .008; anti-PD-1+anti-CTLA-4, OR 2.750, 95%CI [1.471-5.142], *P* = .002). Age <65 years was negatively associated with the risk of death in patients with PD-1 inhibitors or PD-1+CTLA-4 inhibitors (PD-1 inhibitors, OR 0.608, 95%CI [0.458-0.807], *P* = .001; PD-1+CTLA-4 inhibitors, OR 0.575, 95%CI [0.343-0.963], *P* = .035), and with the risk of severe cases in all regimens except PD-1+CTLA-4 inhibitors (PD-1 inhibitors, OR 0.617, 95%CI [0.492-0.774], *P* < .001; PD-L1 inhibitors, OR 0.384, 95%CI [0.227-0.649], *P* < .001; CTLA-4 inhibitors, OR 0.382, 95%CI [0.179-0.812], *P* = .012).

Discussion

Besides the prolonged tumor-killing effect of ICIs through immune activating, ICIs could destroy immune homeostasis and mediate autoimmune adverse effects in various organs, including the endocrine system. Since January 1, 2011 when the first ICI drug (Ipilimumab) obtained approval from the FDA, the cases of ICI-related endocrine toxicities were reported and accumulated. To our knowledge, this study is, to date, the most recent and largest set of clinical characteristics of ICI-TDs using individual adverse events reports from the FDA FAERS database. Our study revealed the increasing incidence of ICI-related hypothyroidism, hyperthyroidism, and thyroiditis, as well as a significantly higher proportion of ICI-associated hypothyroidism compared with the other 2 disease categories.

The incidence of ICI-TDs remained debating in diverse studies. In our study, it was 2.6% in ICI adverse event cases. In a meta-analysis comprising 38 randomized controlled trials (RCTs), the incidence of ICIs-related hypothyroidism was estimated to be 6.6% in all patients on ICIs therapy,[2] and the incidence of ICIs-TDs was even higher in some RCTs.[6] Patients enrolled in RCTs had more frequent follow-up and evaluation of thyroid function, while a proportion of non-serious ICI-TDs cases may not be reported to FAERS and some cases were spontaneous remission in the real world.[4] All the facts resulted in the difference of incidence of ICI-TDs.

The increasing trend of incidence of ICI-TDs may be explained by a more profound and prevalent understanding of the disease by both oncologists and endocrinologists. In a recent couple of years, patients on ICIs therapy were arranged for regular surveillance of thyroid function by the oncologists along with the latest published guidelines for ICI therapy,[7] which may contribute to the increasing diagnosis rate of ICI-TDs by reporting years. Due to the decreasing prescription of anti-CTLA-4 (ipilimumab) mono-therapy and more frequent application of anti-PD-1 + anti-CTLA-4 therapy, the incidence of anti-CTLA-4 mono-therapy induced thyroid dysfunction reduced over time. For the demographic characteristics of ICIs-TDs patients, our study revealed a slightly female predominance on ICIs-TDs in patients receiving anti-PD-1 therapy, anti-PD-L1 therapy, and the combination of anti-PD-1 + anti-CTLA-4 therapy, which was suggested in a systematic review that male had a lower frequency of ICIs-related endocrinopathies, especially thyroid dysfunction, compared with female individuals.[8]

Thyroid function of ICI-TDs was various, from thyrotoxicosis to hypothyroidism, subclinical to overt, even thyrotoxic crisis. Subclinical thyroid dysfunction occurred in up to 50% of ICIs-TDs patients,[3] while it was incapable to distinguish subclinical hypothyroidism or hyperthyroidism using FAERS. Our study discovered that hypothyroidism was seen in 62.0% of patients as the vast majority of case in ICI-TDs, and similar results were reported recently.[9] Our study revealed a higher risk of hypothyroidism in patients on PD-1 inhibitors compared with other regimens, including the combination therapy of anti-PD-1 and anti-CTLA-4, similar with the results of the meta-analysis.[2] However, individuals on anti-PD-1+ anti-CTLA-4 therapy displayed a higher risk of thyroiditis. A retrospective study revealed that 4 of 37 patients with ICI-related hypothyroidism recovered without initiating levothyroxine,[10] indicating a possibility of spontaneous remission of ICI-TDs. In our study, 171 patients (9.3%, 171/1842) presented as hyperthyroidism preceding hypothyroidism, and the dynamic alternation of thyroid function could be explained by destructive thyroiditis caused by ICI treatment.[11] Anti-thyroid antibody could increase in a proportion of ICI-TDs,[12] while data of anti-thyroid antibodies were unavailable in FAERS for further analysis. Our study reported cases of thyrotoxic crisis in 11 patients [5/11 on PD-1 inhibitor (nivolumab) and 6/11 on anti-PD-1 + anti-CTLA-4 therapy (nivolumab-ipilimumab)]. An observational study, of which data were obtained from the WHO Adverse Drug Reaction Database, VigiBase, reported 11 thyrotoxic crisis cases, and 7 of them occurred under ICIs combination therapy.[13] Both studies indicated that ICIs-TDs could induce thyrotoxic crisis and life-threatening clinical outcome, thus a regular measurement of thyroid function should be recommended as a clinical routine for patients on ICIs treatment, in particular those on ICIs combination therapy.

In the aspect of co-occurrence endocrinopathies, we concluded that patients on the combination therapy of anti-CTLA-4 and anti-PD-1 had more likelihood of other immune-related endocrinopathies compared with those on PD-1 or PD-L1 inhibitors, which was in accordance with previous research.[2] This phenomenon might be explicated by the possible destructive potential of anti-CTLA-4 (ipilimumab) and its combination therapy to endocrine glands, including thyroid glands, pituitary, and pancreas β cells. In clinical practice, patients on CTLA-4 inhibitors or its combination therapy should be under more frequent surveillance of thyroid, adrenal, and pituitary function, as well as glucose level, in case of endocrinology irAEs.

Based on the Common Terminology Criteria for Adverse Events (CTCAE) criteria, adverse events of thyroid dysfunction were graded from 1 to 5.[14] Previous study reported that the majority of anti-PD-1 agents induced thyroid dysfunction was graded 1/2, while grade 3/4 (severe/life-threatening) was reported in 15% of patients with thyroid dysfunction on anti-PD-1 monotherapy.[15] Anti-CTLA-4 or anti-PD-1 mono-therapy had a lower occurrence of grade 3/4 adverse events compared with anti-PD-1+anti-CTLA-4 combination therapy.[16-18] FAERS database did not report adverse events by grade, while we analyzed the clinical outcomes of patients with ICIs-TDs on different ICIs therapy compared with all cases with ICIs-related adverse events. We indicated that patients on anti-PD-1 + anti-CTLA-4 therapy showed a higher risk of severe cases compared with all mono-therapy, while patients on anti-PD-1 therapy had a higher risk of death compared with other regimens.

We further analyzed the risk factors of death or severe cases including age, regimens, and cancer type. Patients with melanoma were related to the risk of death when they were put on the combination therapy of anti-PD-1+anti-CTLA-4. One

possible explanation was that patients with advanced melanoma were preferred to the application of combined therapy of anti-tumor drugs including ICIs,[6] which contributed to a higher risk of adverse event and poor prognosis. Younger age (age< 65 years) was another factor of better prognosis in patients on different ICI regimens. While younger age is related to better clinical outcomes in many situations, this is the first report of younger age as a better prognosis factor in patients on ICIs. The risk of severe cases in individuals on PD-1 inhibitors or CTLA-4 inhibitors increased when they developed hypothyroidism, and other endocrinology comorbidities was another positive factor of the outcome of severe cases in patients receiving anti-PD-1, anti-PD-L1, or anti-PD-1 + anti-CTLA-4 therapy. Interestingly, the development of other endocrinology comorbidities was a protective factor of death in patients on anti-PD-1 or anti-PD-1 + anti-CTLA-4 therapy. Several observational studies indicated that both progression-free survival and overall survival were improved after the occurrence of thyroid irAE, especially in patients with overt hypothyroidism,[19-21] which was different from our study. Researchers postulated that the development of irAE might reflect the efficacy of antitumor in patients on ICIs therapy, which led to a better prognosis with a proportion of immortal time bias, though.[22] This hypothesis could explain the phenomenon that the immune-related endocrinopathies, including hypothyroidism or hyperthyroidism, were positively associated with the risk of severe cases due to the emerging clinical manifestations of thyroid function alteration, which could result in hospitalization. Patients on ICIs therapy, who were more vulnerable to irAEs, were also a better response to the antitumor effect of ICIs, which may contribute to the lower death rate. Because the FAERS database was established from mainly clinical practice, a part of nonserious cases in the real world maybe not reported and included in the database. Also, the cases of death in FAERS resulted from all causes including adverse events and advanced tumor, which might contribute to a higher risk of death than RCTs. It was important that ICIs-mediated adverse events, accompanied with ICI therapy starting anti-tumor effect, could bring about or contribute to the poor clinical outcome of the reported cases. Therefore, these endocrinologic irAEs, which are easy to be monitored as thyroid function, are critical clues for clinicians to pay more attention to. Once the situation of endocrinologic irAEs happens, clinicians may adjust the treatment in time while alert to serious adverse events or clinical outcomes.

As a retrospective study rather than a prospective study, the limitations are associated with our data resource solely from the reported cases in the FAERS database, which was a voluntary adverse event reporting system that included only part of ICI-TD cases and could cause referral bias, nor is the database able to be checked in detail. The dosing and frequency of the drugs were not documented in FAERS, thus the dose-effect relationship of irAEs could not be analyzed. Also, the subtypes of ICI-TDs were based on reported diagnosis and diagnosis code terms. There was bias during statistical analysis due to the overlap between abnormal thyroid function and thyroiditis in the FAERS database. To avoid duplicate category, only thyroiditis without thyroid function information was categorized to the group of thyroiditis, which may lead to the underestimated occurrence rate of thyroiditis. In addition, our study focused on ICIs-mediated new-diagnosed thyroid dysfunction rather than pre-existing thyroid abnormalities, which brought about bias to prognosis analysis.

Conclusions

Thyroids dysfunction is the most common endocrine irAE after ICI treatment. A combined regimen of anti-PD-1 + anti-CTLA-4 results in a higher possibility of thyroiditis and other endocrinopathies, while mono-therapy of PD-1 inhibitor leads to an elevated risk of hypothyroidism. Regular monitor of thyroid function is indispensable, since ICI-TDs manifested as hyperthyroidism followed by hypothyroidism, and could lead to thyrotoxic crisis and death. Awareness among health care professionals is critical when hypothyroidism occurs, which may indicate poor clinical outcomes.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conception/design: Y.G, J.Z., X.G.; Provision of study material or patients: D.L, Y.G; Collection and/or assembly of data: D.L, Y.G; Data analysis and interpretation: D.L., Y.G.; Manuscript writing: D.L, Y.G; Final approval of manuscript: J.Y., G.Y., J.Z., X.G., Y.G.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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