Thyroid dysfunction after immune checkpoint inhibitor treatment in a single-center Chinese cohort: a retrospective study

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Research Article

Keywords:

Posted Date: November 9th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2210602/v1

Abstract

Background

Thyroid dysfunction is a common adverse event after immune checkpoint inhibitor (ICI) therapy. The clinical manifestations of thyroid immune-related adverse events (irAEs) are variable and the underlying mechanism is unclear.

Purpose

To identify the clinical and biochemical characteristics of Chinese patients with ICI-related thyroid dysfunction.

Methods

We retrospectively reviewed patients with carcinoma who received ICI therapy and underwent evaluation of thyroid function during hospitalization at Peking Union Medical College Hospital between January 1, 2017 and December 31, 2020. Clinical and biochemical features were analyzed in patients who developed ICI-related thyroid dysfunction. Survival analyses were performed to determine the effect of thyroid autoantibodies on thyroid abnormalities and the impact of thyroid irAEs on clinical outcomes.

Results

The cohort included 270 patients with a median follow-up of 17.7 months; 120 (44%) of these patients developed thyroid dysfunction on immunotherapy. The most common thyroid irAE was overt hypothyroidism (with/without transient hyperthyroidism), which occurred in 38% of patients (n = 45), followed by subclinical thyrotoxicosis (n = 42), subclinical hypothyroidism (n = 27), and isolated overt thyrotoxicosis (n = 6). The median time to onset was 49 days (interquartile range 23, 93) for thyrotoxicosis and 98 days (interquartile range 51, 172) for hypothyroidism. In patients treated with PD-1 inhibitors, hypothyroidism was strongly associated with younger age (odds ratio [OR] 0.44, 95% confidence interval [CI] 0.29–0.67; P < 0.001), previous thyroid disease (OR 4.30, 95% CI 1.54–11.99; P = 0.005), and a higher baseline thyroid-stimulating hormone level (OR 2.76, 95% CI 1.80–4.23; P < 0.001). Thyrotoxicosis was only associated with the baseline thyroid-stimulating hormone (TSH) level (OR 0.59, 95% CI 0.37–0.94; P = 0.025). Thyroid dysfunction after initiation of ICI therapy was associated with better progression-free survival (hazard ratio [HR] 0.61, 95% CI 0.44–0.86; P = 0.005) and overall survival (hazard ratio 0.67, 95% CI 0.45–0.99; P = 0.046). Anti-thyroglobulin antibody positivity increased the risk of thyroid irAEs.

Conclusions

Thyroid irAEs are common and have diverse phenotypes. Heterogeneity between thyrotoxicosis and hypothyroidism is arising with distinct clinical and biochemical characteristics. The pathogenesis of thyroid irAEs warrants further research.

Introduction

Immunotherapy is a recent breakthrough in the treatment of malignant tumors and is now widely used in clinical practice. As the best applications of immunotherapy, immune checkpoint inhibitors (ICIs) activate T lymphocytes by blocking the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) or programmed death receptor 1 (PD-1) /programmed death-ligand 1 (PD-L1) pathway to destroy tumor cells[1, 2]. At the same, normal organs and systems can also be targeted, producing immune-related adverse events (irAEs). The incidence of irAEs is highest in the endocrine system, where the most common irAE is thyroid dysfunction[3]. Since the approval of nivolumab by the National Medical Products Administration of China in June 2018, other ICIs, including pembrolizumab, camrelizumab, sintilimab, tislelizumab, durvalumab, and atezolizumab, have been approved in China. According to data from the Peking Union Medical College Hospital (PUMCH), ICI-related thyroid dysfunction is the most frequent irAE in China and had an incidence of 7.2% in 1905 patients with lung cancer[4].

The etiology of ICI-related thyroid dysfunction has generally been assumed to be immune-mediated destructive thyroiditis, with transient thyrotoxicosis initially that subsequently changes to hypothyroidism. The interval between initiation of an ICI and onset of thyroid abnormalities is usually a couple of months. The spectrum of ICI-related thyroid dysfunction is variable and includes isolated thyrotoxicosis or hypothyroidism as well as subclinical thyroid dysfunction[5]. Thyroid autoantibodies have been observed in patients with thyroid irAEs. An association has been reported between thyroid peroxidase antibody (TPOAb) or anti-thyroglobulin antibody (TgAb) positivity after initial treatment with an ICI and emergence of thyroid dysfunction[6, 7]. TgAb positivity at baseline significantly increases the risk of developing thyroid irAEs and shortens the time to onset of thyroid dysfunction. [8] However, there is no evident association between thyroid autoantibodies and the pathogenesis of ICI-related thyroid dysfunction[8–10]. The clinical outcomes in patients with malignancy can be improved by treatment with ICIs [11], and several observational studies have indicated that thyroid toxicity is associated with better progression-free survival (PFS) and overall survival (OS) in these patients[12–14]. However, there is no strong evidence to support this suggestion or any relevant data in China.

In view of the lack of studies in Chinese patients with ICI-associated thyroid dysfunction, this study aimed to describe the spectrum of ICI-related thyroid dysfunction and investigate similarities and differences of characteristics in Chinese with research from other regions.

Materials And Methods

Study Population

Information on thyroid function in patients hospitalized with malignant carcinoma between January 1, 2017 and December 31, 2020 was obtained from the PUMCH medical records database. A total of 425 cases were identified to have been treated with ICIs during the study period. The frequency of serum thyroid function was at subsequent ICI doses every 3–4 weeks. In patients with documented thyroid dysfunction, testing was performed more frequently on an individualized basis. Patients who received at least one dose of an ICI and underwent one further measurement of thyroid function following the first ICI dose were included in the study. Patients were excluded if they were identified to have a non-ICI-related thyroid function abnormality, such as central hypothyroidism, thyroid binding globulin deficiency, non-thyroidal illness syndrome, radiotherapy-related thyroiditis, or unexplained thyroid biochemistry.

Definitions

A thyroid irAE was defined as detection of new-onset thyroid dysfunction after immunotherapy and subcategorized by the biochemical pattern of thyroid dysfunction. Overt thyrotoxicosis was defined as a TSH level below the lower reference limit and a free thyroxine (FT4) level above the upper reference limit. Subclinical thyrotoxicosis was defined as a TSH level below the lower reference range without an abnormal serum FT4 concentration. Overt hypothyroidism was defined as a TSH level over the upper reference range with a FT4 level below the lower reference interval or a TSH level > 10.0 μIU/mL regardless of the FT4 level. Subclinical hypothyroidism was defined as elevation of TSH over the upper limit of the normal reference range and < 10.0 μIU/mL accompanied by a normal FT4 level.

Time to onset of thyroid dysfunction was determined as the interval between the initial dose of ICI therapy and the first documented thyroid function abnormality. The duration of thyrotoxicosis or hypothyroidism was defined as the time to restoration of normal TSH following the first laboratory-documented thyroid function abnormality. Pre-existing thyroid disease included a past history of thyroiditis without hypothyroidism or controlled Graves' disease documented in the medical records.

The tumors in our cohort were divided into lung cancer and other types of tumor. Other tumor types included colorectal carcinoma, gastric carcinoma, esophageal carcinoma, liver cancer, gallbladder cancer, renal carcinoma, bladder carcinoma, ureteral cancer, choriocarcinoma, ovarian cancer, endometrial cancer, and non-Hodgkin lymphoma. Tumor progression was classified according to the Response Evaluation Criteria in Solid Tumors. OS was defined as the time interval between the first ICI dose and either the date of death or the date of last follow-up. PFS was defined as the time interval between initiation of ICI therapy and disease progression for the first time or death.

Assay Characteristics

The PUMCH laboratory has the following established reference ranges for thyroid function parameters: free triiodothyronine (FT3), 1.80–4.10 pg/mL; triiodothyronine (T3), 0.66–1.92 ng/mL; FT4, 0.81–1.89

ng/dL; tetraiodothyronine (T4), 4.30–12.50 μg/dL; and TSH, 0.38–4.34 μIU/mL. A TPOAb level of > 34 IU/mL and a TgAb level of > 115 IU/mL are considered positive.

Serum thyroid hormone concentrations were measured using specific chemiluminescence immunoassays (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). TPOAb and TgAb levels were measured using Roche kits and the included reagents (Cobas e601, Roche Diagnostics, Mannheim, Germany) according to the manufacturer's instructions.

Statistical Analysis

Continuous variables with a normal distribution are summarized as the mean ± standard deviation and compared between groups using the *t*-test or rank-sum test. Outcome variables that were not normally distributed are shown as the median and interquartile range (IQR) and compared between groups using the Mann–Whitney *U* test. Categorical variables are reported as the frequency and percentage and compared between groups using Pearson's chi-squared test and Fisher's exact test. Associations between demographic factors and thyroid irAEs were assessed using a multivariable logistic regression model that included all factors with a P-value < 0.10 in univariate analysis. The results of multifactorial logistic regression analysis are presented as the odds ratio (OR) and 95% confidence interval (CI). Kaplan–Meier survival curves were used to analyze the significance of a past history of thyroid disease, TgAb, TPOAb, PFS, and OS, in terms of the occurrence of thyroid irAEs. Differences in survival rates between subgroups were compared using the log-rank test. The effect of thyroid irAEs on OS and PFS was estimated by Cox regression adjusted or age, sex, and tumor stage. All statistical tests were two-tailed with the two-sided statistical significance level set at P = 0.05. The statistical analysis was performed using SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Figures were created using GraphPad Prism version 8 (GraphPad Software, San Diego, CA, USA).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the PUMCH Ethics Committees (No. ZS-3587). Informed consent was not required because all the study parameters were routinely obtained at the time of the study and no additional investigations or procedures were carried out.

Results

Patient Characteristics

A total of 425 inpatients with malignant tumors were treated with ICIs at PUMCH during the study period. Patients with incomplete information (n = 127), pre-existing hypothyroidism or levothyroxine replacement before initiation of ICI therapy (n = 11), or other factors known to contribute to thyroid dysfunction after immunotherapy (n = 17) were excluded (Fig. 1). Therefore, 270 patients were included in the study. Lung cancer was the most common type of tumor (n = 221, 81%). The median age at the time of initiation of ICI therapy was 64 years (IQR 57, 69). Most patients in the cohort were male (n = 192, 71%). Almost all

patients (n = 264, 97%) received anti-PD-1 antibodies therapy (pembrolizumab/sintilimab/nivolumab/camrelizumab/tislelizumab) or PD-L1 antibodies therapy (durvalumab/atezolizumab/sugemalimab [under clinical investigation]). Only seven patients (3%) received a combination of an anti-CTLA-4 antibody (ipilimumab/tremelimumab) and anti-PD-1/PD-L1 antibodies (pembrolizumab/nivolumab/durvalumab). One patients received KN044 (under clinical investigation) alone. The baseline information is shown in Table 1.

Table 1
Baseline Characteristics

		All patients	Thyroid irAE	No thyroid irAE	P value
Numbers (%)		270 (100)	120 (44)	150 (56)	/
Average Age(IQR)		64 (57, 69)	63 (55, 68)	65 (59, 69)	0.042
Sex	Male(%)	192 (71)	81 (68)	111(74)	0.242
	Female(%)	78 (29)	39 (33)	39(26)	
ICI types	CTLA-4(%)	1 (0)	1(1)	0(0)	0.136
	PD-1/PD-L1(%)	262(97)	114(95)	148(99)	
	Combination of CTLA-4 + PD-1/PD-L1(%)	7(3)	5(4)	2(1)	
Tumor types	Lung cancer (%)	220 (81)	93 (78)	127 (85)	0.132
	Other tumors (%)	50 (19)	27 (23)	23 (15)	
Tumor Stage (AJCC)	I -III(%)	62 (23)	29 (24)	33 (22)	0.709
	IV (%)	208 (77)	91 (75)	117 (78)	
Previous thyroid disease (%)		44 (16)	26 (21)	18 (12)	0.033
Other irAEs (%)		49 (18)	23 (19)	26 (17)	0.698
Long-term heavy smoking (%)		146 (54)	61 (50)	85 (57)	0.319
TSH (μIU/ml) (median, IQR)		1.5 (0.8, 2.3)	1.7 (0.9, 2.7)	1.4 (0.8, 2.1)	0.064
TPOAb positive (%)		20/114 (18)	15/69 (22)	5/45 (11)	0.145
TgAb positive (%)		24/114 (21)	20/69 (29)	4/45 (9)	0.010

IQR, interquartile range; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed death receptor 1; PD-L1, programmed death-ligand 1; ICI, immune checkpoint inhibitors; AJCC, American joint Committee on cancer; irAE, immune-related adverse events; TSH, thyroid-stimulating hormone; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody.

Incidence And Spectrum Of Thyroid Dysfunction

During follow-up, 120 patients (44%) developed ICI-related thyroid dysfunction. The median age at onset was 63 years (IQR 53, 68). One hundred and sixteen (44%) of the 264 patients treated with anti-PD-1/PD-

L1 antibodies developed thyroid irAEs.

The spectrum of abnormal thyroid function was variable. Primary hypothyroidism (including transient thyrotoxicosis with subsequent conversion to hypothyroidism) was the most common thyroid irAE, occurring in 74 patients (61%); 43 (58%) developed overt hypothyroidism and the remaining 31 cases (42%) were subclinical. What different in primary hyperthyroidism is that most cases were subclinical thyrotoxicosis (41/48, 85%). Only seven patients (15%) developed overt thyrotoxicosis alone (Table 2); two of these patients were tested for TSH receptor antibodies but neither was positive.

Table 2
Clinical features of thyroid dysfunction in patients with thyroid immune-related adverse events

		Thyrotoxicosis		Hypothyroidism		P value
		Subclinical	Overt	Subclinical	Overt	
Patients		42 (35)	6 (5)	27 (23)	45 (38)	/
Age (IQR)		66 (60, 70)		60 (54, 66)		0.002
Sex	Male (%)	33 (28)		48 (40)		0.811
	Female (%)	15 (13)		24 (20)		
ICI types	CTLA-4	0 (0)		1(1)		0.788
	PD-1/PD-L1	47 (39)		67 (56)		
	CTLA-4 + PD-1/PD-L1	1 (1)		4 (3)		
Tumor type	Lung cancer (%)	44 (37)		49 (41)		0.002
	Other tumors (%)	4 (8)		23 (32)		
Tumor Stage (AJCC)	I-III (%)	8 (17)		21 (29)		0.311
	IV (%)	40 (33)		51 (43)		
Days to onset (median, IQR)		51 (22–92)	30 (25–58)	152 (43–263)	88 (55–141)	0.002
Transient thyrotoxicosis	Number (%)	/		20 (28)		/
	Days to hypothyroidism (IQR)	/		47 (30,91)		
Baseline TSH (μIU/ml) (median, IQR)		1.0 (0.5, 1.8)		2.3 (1.5, 3.1)		< 0.001
TPOAb positive (%)		4/36 (11)		11/33 (33)		0.025
TgAb positive (%)		4/36 (11)		16/33 (48)		0.001
Previous thyroid disease (%)		7 (6)		19 (16)		0.124
Other irAEs (%)		7 (6)		15 (13)		0.386
Long-term heavy smoking (%)		26 (21)		35 (29)		0.522

IQR, interquartile range; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; PD-1, programmed death receptor 1; PD-L1, programmed death-ligand 1; ICI, immune checkpoint inhibitors; AJCC, American joint Committee on cancer; irAE, immune-related adverse events; TSH, thyroid-stimulating hormone; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody.

Kinetics Of Thyroid Dysfunction

There were no severe thyroid irAEs (grade 3–4 according to the Common Terminology Criteria for Adverse Events) in any of the patients with thyroid dysfunction. The median number of treatment courses at the time of onset of thyroid dysfunction was 3 (IQR 1, 5). The median time to onset of thyrotoxicosis was significantly shorter than that to onset of hypothyroidism (49 days [IQR 23, 93] versus 98 days [IQR 51, 172]; P < 0.001). Twenty (27%) of the 74 patients who developed hypothyroidism experienced a classical thyroiditis-like pattern of transient thyrotoxicosis at a median of 47 days (IQR 29, 74) before onset of hypothyroidism. Among the patients who developed hypothyroidism, the shortest time to onset was 10 days and the longest was 502 days; all of these were cases of subclinical hypothyroidism. However, the time to onset of thyrotoxicosis ranged from 11 days to 387 days. Five patients developed abnormal thyroid function more than 1 year after initiation of ICI therapy; the thyroid dysfunction was subclinical in four of these cases. Seventeen (63%) of 27 patients with subclinical hypothyroidism eventually returned to normal thyroid function and seven patients had not retested. The median time to onset was longer for subclinical thyrotoxicosis and hypothyroidism than for overt thyroid disorders (80 days [IQR 45, 122] vs 71 days [IQR 28, 160]; P = 0.525). There was no significant difference in time to onset among the subclinical and overt subgroups (thyrotoxicosis: 30 days [IQR 25, 58] vs 51 days [IQR 22, 92], P = 0.374; hypothyroidism: 88 days [IQR 55, 141] vs 152 days [IQR 43, 263], P = 0.159).

Among the patients with overt hypothyroidism, the median maximum TSH level was 80.8 μIU/mL (IQR 29.6, 113.8). There were 29 records of levothyroxine replacement in patients with overt hypothyroidism (at a mean dose of 1.3 ± 0.6 μg/kg/day). Thirty-two (76%) of 42 patients with subclinical thyrotoxicosis recovered normal thyroid function during follow-up whereas in patients with overt thyrotoxicosis, 3/6 (50%) returned to normal level during follow-up and two patients did not have further laboratory tests. Only one patient with subclinical thyrotoxicosis did not recover normal thyroid function. The median maximum FT4 level in patients with overt thyrotoxicosis was 2.8 ng/dL (IQR 2.3, 3.0). None of these patients were prescribed anti-thyroid drugs or glucocorticoids.

Clinical Features And Biomarkers

To control the variant of different ICI types, this section presents information only for the subset of 262 patients who received anti-PD-1/PD-L1 antibodies. There was a negative association of ICI-related thyroid dysfunction with age (OR 0.76 per 10 years; 95% CI 0.56–1.03; P = 0.072); this finding was not statistically significant. However, hypothyroidism was significantly more common in younger patients (OR 0.44 per 10 years; 95% CI 0.29–0.67; P < 0.001). Patients with a past history of thyroid disease were at increased risk of thyroid irAEs (OR 2.26; 95% CI 1.06–4.84; P = 0.036), especially in patients who presented hypothyroidism (OR 4.30; 95% CI 1.54–11.99; P = 0.005). Thyrotoxicosis could not be predicted by age or past history (Table 3). Survival analyses were performed separately for patients who developed thyroid irAEs and those who developed hypothyroidism. Patients with a past history of thyroid disease had a significantly shorter time to onset of thyroid irAEs (P = 0.008, log-rank test), especially

hypothyroidism (P < 0.001, log-rank test;) than those with no history of thyroid disease (Fig. 2). The median time to onset of thyroid irAEs was 3.3 months in patients with a past history of thyroid disease; by 5 months, the incidence of thyroid irAEs was 46% in these patients.

Table 3
Demographic characteristics of patients with PD-1/PD-L1 associated thyroid dysfunction versus normal thyroid dysfunction during follow-up

Factor	Any thyroid irAE OR (95%CI)	P value	Thyrotoxicosis OR (95%CI)	P value	Hypothyroidism OR (95%CI)	P value
Age (per 10 years)	0.76 (0.56–1.03)	0.072	1.27 (0.82–1.95)	0.280	0.44 (0.29–0.67)	< 0.001
Previous thyroid disease	2.26 (1.06–4.84)	0.036	1.55 (0.57–4.20)	0.387	4.30 (1.54–11.99)	0.005
Baseline TSH (per 1μIU/ml)	1.33 (1.00-1.77)	0.047	0.59 (0.37–0.94)	0.025	2.76 (1.80–4.23)	< 0.001
OR, odds ratio; TSH, thyroid-stimulating hormone.						

The baseline TSH level could predict thyroid irAEs (OR 1.33 per μIU/mL; 95% CI 1.00–1.77; P = 0.047), especially in patients with hypothyroidism (OR 2.76 per μIU/mL; 95% CI 1.80–4.23; P < 0.001). Receiver-operating characteristic curve analysis showed that baseline TSH values greater than 2.01 μIU/mL were 72% specific and 42% sensitive for prediction of subsequent primary hypothyroidism.

Thyroid Autoantibodies

One hundred and fourteen patients had TPOAb and TgAb test results available during follow-up. Twenty-eight patients (25%) were positive for TPOAb, TgAb, or both. Among 45 patients who maintained normal thyroid function, five (11%) were positive for TPOAb and four (9%) were positive for TgAb (Table 1). Among patients with positive autoantibodies, 7/20 (35%) had TPOAb and 5/24 (21%) had TgAb at baseline; only 3/20 (15%) TPOAb and 4/24 (17%) TgAb emerged after ICI therapy. Nevertheless, in patients with thyroid irAEs, the TPOAb and TgAb positivity rates were 22% and 29%, respectively. Thirteen of the patients with thyroid irAEs were positive for both TPOAb and TgAb and only three were euthyroid. The prevalence of TgAb positivity was higher in patients with thyroid dysfunction, especially in those with hypothyroidism (Tables 1 and 2). In patients with overt thyroid abnormalities, 12/30 (40%) were positive for both TPOAb and TgAb, whereas only 1/39 (3%) with subclinical thyroid disorders was positive for both antibodies. The proportions of TPOAb and TgAb positivity were significantly different between

subclinical thyroid dysfunction and overt thyroid dysfunction (TPOAb, 3% vs 47%, P < 0.001; TgAb, 5% vs 60%, P < 0.001).

Survival analysis was used to investigate the effect of thyroid autoantibodies on the risk of development of thyroid irAEs. The risk of thyroid dysfunction after immunotherapy was significantly increased by TgAb (P = 0.002, log-rank test) positivity (Fig. 3).

Prognostic Significance

The data presented in this section are for the 262 patients treated with anti-PD-1/PD-L1 antibodies, for controlling the effect of different types of ICIs. In this subgroup, the median follow-up duration was 17.5 months (IQR 9.0, 23.9). There was no significant difference in the tumor progression rate according to the Response Evaluation Criteria in Solid Tumors (75.4% vs 71.4%; P = 0.51) or the mortality rate (48.0% vs 40.7%; P = 0.24) between patients who remained euthyroid after initiation of ICI therapy and those who developed thyroid irAEs.

According to the results of the survival analysis, patients who developed thyroid dysfunction during immunotherapy had longer PFS (P = 0.013, log-rank test) and OS (P = 0.024, log-rank test) than those who remained euthyroid. These findings were in accordance with those of the multivariable Cox regression analysis (adjusted for age, sex, tumor stage, and tumor type) for PFS (HR 0.61, 95% CI 0.44–0.86; P = 0.005) and OS (HR 0.67, 95% CI 0.45–0.99; P = 0.046).

Discussion

This single-center retrospective study includes the largest cohort of patients with ICI-related thyroid dysfunction analyzed in China to date. The prevalence of thyroid dysfunction in this study was similar to that in the largest cohort study reported at present[15] but higher than that in an east Asian cohort[16–19]. Our study aimed to describe the clinical and biochemical features of the different types of thyroid dysfunction that can occur in patients on ICI therapy and found that the etiology of subclinical thyroid dysfunction could be different from that of overt thyroid abnormalities.

In terms of clinical factors relevant to thyroid irAEs, age was an independent risk factor for the development of ICI-related hypothyroidism (with or without transient thyrotoxicosis) in our cohort; this finding is consistent with that in the largest cohort reported to date [15]. Compared with the same study, female sex was not found to be a risk factor for thyroid dysfunction, but similar to other reports of anti-PD-1 antibodies associated thyroid dysfunction in patients with lung cancer[16, 20], which may be limited because of our smaller sample size and lung cancer being the predominant tumor type.

There was heterogeneity in kinetics between the different types of abnormal thyroid function. The median time to onset was significantly shorter for thyrotoxicosis than for hypothyroidism (49 days vs 98 days). These times to onset are slightly longer than those previously reported[6, 9, 21], which may reflect the fact

that thyroid function was not monitored regularly in some patients. Although there was no significant difference in median time to onset between subclinical and overt thyroid dysfunction, the range of time to onset varied between subgroups. Ninety-three percent of the patients who developed subclinical thyrotoxicosis did so within 25 weeks of initiation of immunotherapy, whereas isolated overt thyrotoxicosis usually developed within the first 6 weeks. However, the time to development of hypothyroidism ranged from 10 days to almost one year in 93% of cases. In the subset of patients with overt hypothyroidism, the time to onset was also more widely dispersed, ranging from 3 to 34 weeks. The proportion of patients who developed typical thyroiditis with brief thyrotoxicosis followed by conversion to hypothyroidism was not high, and the median duration of transient thyrotoxicosis was 7 weeks; these findings are comparable with those previous reported[9]. Hence, overt hypothyroidism without a preceding hyperthyroidism phase can be the first manifestation of thyroid irAEs. Furthermore, most patients with subclinical thyroid dysfunction tended to remain euthyroid. Only six patients developed isolated overt thyrotoxicosis and tended to recover normal thyroid function eventually. Overt hypothyroidism requires levothyroxine replacement therapy.

The contribution of antithyroid antibodies to the pathogenesis of thyroid irAEs is unclear[5]. Although TgAb positivity at baseline markedly increased the risk of thyroid irAEs in previous studies[8, 19], our results cannot be considered reliable because of the inadequacy of the baseline data for thyroid autoantibodies. However, we found an increased risk of thyroid irAEs in patients with TgAb positivity after initiation of immunotherapy, which is to some extent consistent with previous findings[6, 19]. Therefore, the prevalence of patients with thyroid autoantibodies needs to be validated in further research.

In our study, positivity for both TPOAb and TgAb was more common in patients with overt thyroid dysfunction than in those with subclinical thyroid disorders or euthyroidism. The elevated baseline TSH levels in our patients with thyroid irAEs, particularly overt hypothyroidism, are consistent with the findings of previous studies[15, 22, 23]. Furthermore, the cut point on our receiver-operating characteristic curve that predicted significant hypothyroidism also coincides with that reported in a previous review[5]. These findings suggest that pre-existing thyroid autoimmunity may increase the risk of ICI-related thyroid toxicity in the future. Moreover, in our study, 11 of 14 patients with thyroiditis-like manifestations were positive for thyroid autoantibodies. These findings indicate that the mechanism of ICI-associated thyroiditis may be similar to that of Hashimoto's thyroiditis, which is mediated by infiltration of thyroid lymphocytes and consequent destruction of thyroid cells [24]. In regard to the underlying mechanism, Yasuda et al. created an animal model of thyroid irAEs using mice pre-immunized with thyroglobulin and found that $CD4^+$ T cells infiltrated the thyroid tissues of mice with thyroid irAEs, indicating that $CD4^+$ T cells are required for development of thyroid irAEs[25]. However, the same conclusion has not been confirmed in humans. Overall, thyroid irAEs are the result of an immune response that needs further investigation.

We found that a past history of thyroid disease, such as Graves' disease or subclinical Hashimoto's thyroiditis, was an independent risk factor for the development of thyroid irAEs, especially ICI-associated hypothyroidism, suggesting that thyroid irAEs may be the result of accelerated potent thyroid disease.

There have been several reports of exacerbation of extrathyroidal autoimmune disease after treatment with PD-1 antibodies[26–29]. Therefore, it is uncertain whether PD-1 antibodies exacerbate underlying autoimmune disease or induce new-onset thyroid dysfunction. Furthermore, we found no correlation between extrathyroidal irAEs and ICI-related thyroid dysfunction in our cohort. This finding is not compatible with those in previous large cohorts[15], probably because of our smaller sample size and inconsistent subgroup classification criteria.

Recent studies have demonstrated improved PFS and OS in patients who develop thyroid irAEs[14, 30–32], which is consistent with our results. Moreover, all types of irAEs have been associated with better OS and PFS[33, 34]. This finding could provide clues that help to unravel the pathogenesis of irAEs. We hypothesize that activation of T-cell function after PD-1 inhibitors therapy may not only increase the likelihood of irAEs but also enhance the anti-tumor response. Further research is needed to confirm this theory.

This study has some of the limitations inherent in all retrospective studies. First, not all patients were tested for thyroid function every 3–4 weeks, which may have resulted in the actual times to onset being longer than occurred. Furthermore, several patients were treated with ICIs for a short period and then changed to other therapeutic regimens without regular monitoring of thyroid function; therefore, some cases of thyroid dysfunction may have been missed. Second, the most common tumor type in our cohort was lung cancer, and most patients with this disease are treated with anti-PD-1 antibodies. Therefore, no conclusions can be drawn regarding occurrence of thyroid irAEs according to type of tumor or type of ICI.

In conclusion, this retrospective study has demonstrated the clinical and biochemical features of ICI-related thyroid dysfunction in Chinese patients, which are generally in accordance with those of previous studies in other regions. In this study, age, past history of thyroid disease, the baseline TSH level, and thyroid autoantibodies status were associated with development of thyroid irAEs, suggesting that the mechanism underlying thyroid dysfunction after ICI therapy is complex and diverse.

Declarations

Author contributions

Xinqi Cheng, Yan Xu, Xiang Wang, Yingyi Wang, Xinrong Fan, Haitao Zhao, Li Zhang, Mengzhao Wang, Xiaofeng Chai and He Liu provided the raw data. Yuelun Zhang conducted the statistical analysis. The first draft of the manuscript was written by Lingge Wu and Naishi Li, Hui Pan and Xiaolan Lian edited and guided writing of the manuscript. Naishi Li, Hui Pan and Xiaolan Lian are co-corresponding authors. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

This work was funded by grants from the Chinese Academy of Medical Sciences (CAMS) Innovation Fund for Medical Science (CIFMS; No. 2021-1-I2M-022). The authors thank all patients for participating the study.

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Figures

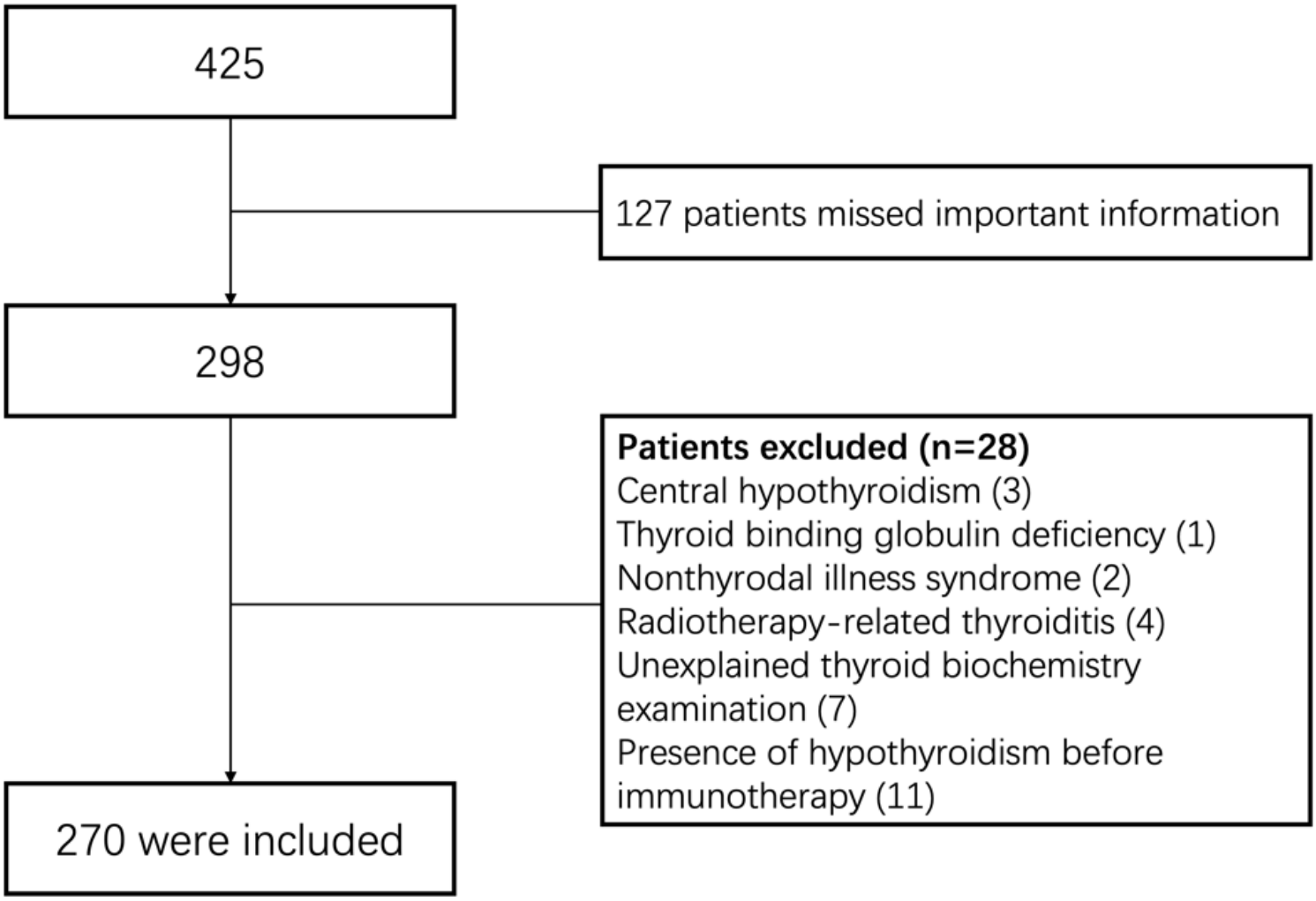

Figure 1

Flowchart of patients selected

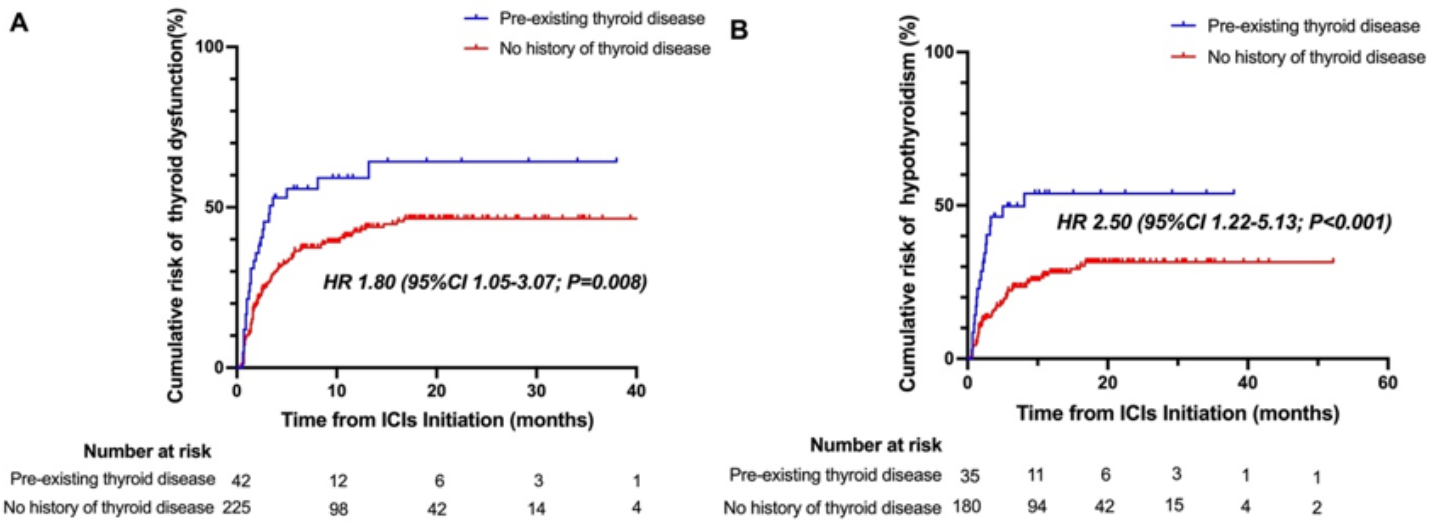

Figure 2

Cumulative risk of thyroid dysfunction (A) and hypothyroidism (B) in patients with previous thyroid disease after anti-PD-1/PD-L1 antibodies therapy

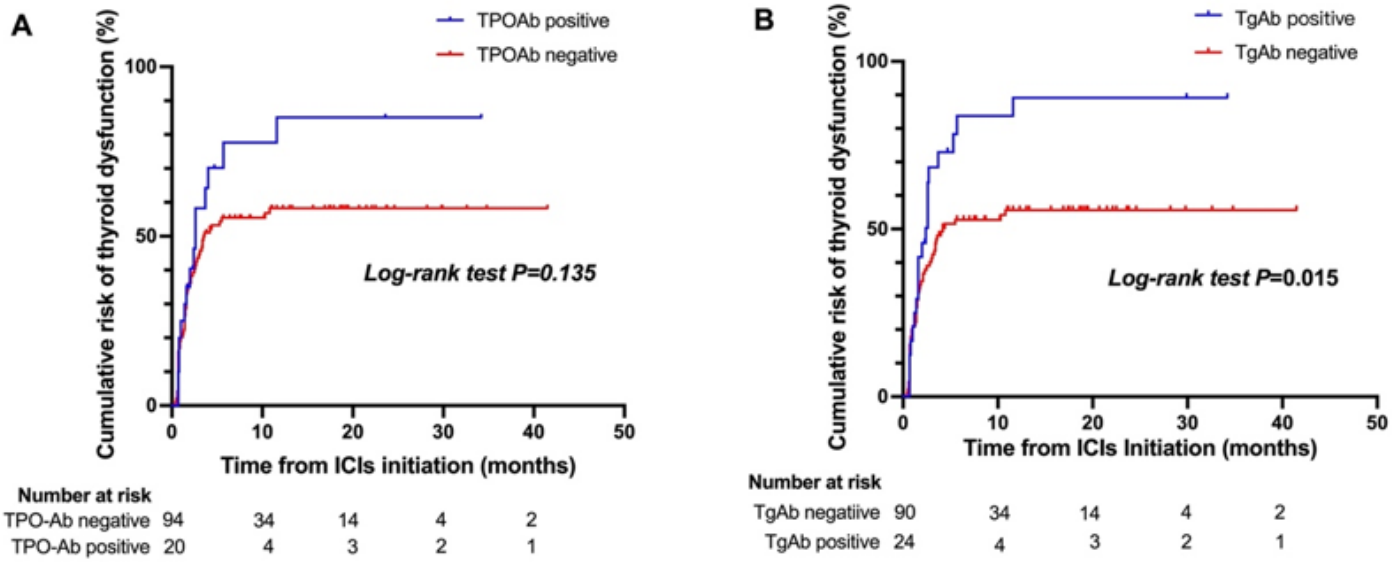

Figure 3

Posibility of ICI-related thyroid dysfunction of patients with TPOAb (A) and TgAb (B)

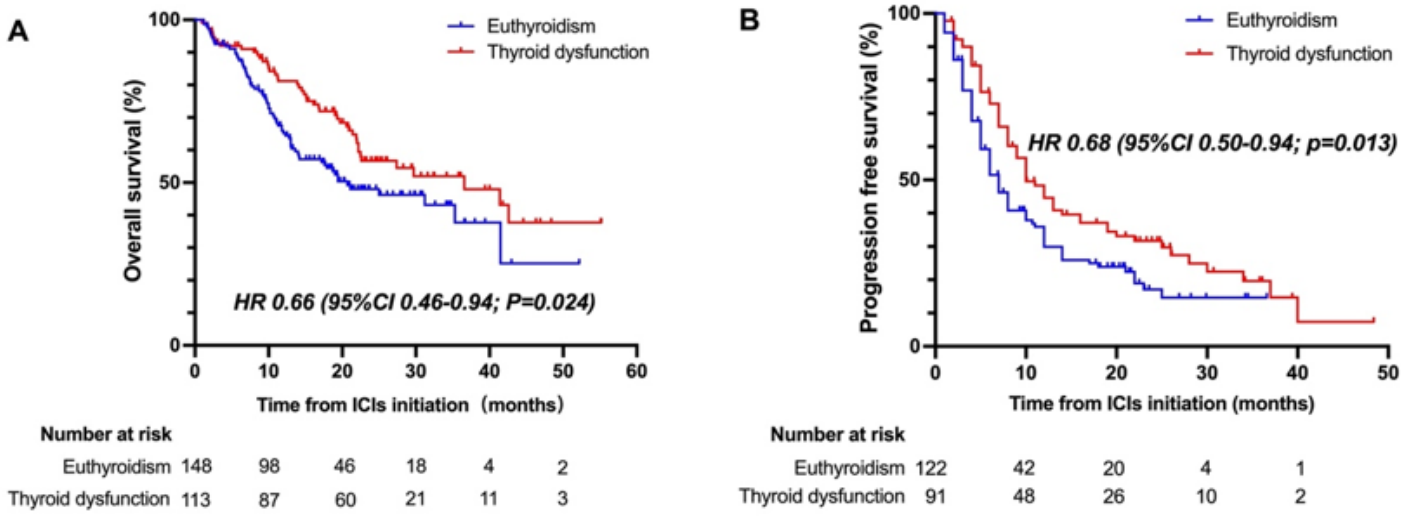

Figure 4

Overall survival (A) and progression free survival (B) in patients with thyroid dysfunction after anti-PD-1/PD-L1 antibodies therapy