



Immune-related thyroid dysfunction in patients with non-small cell lung cancer

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Background: Immune-related thyroid dysfunction (irTD) is a common immune-related adverse event (irAE). The potential biomarkers of irTDs and their impact on the clinical outcomes of patients with non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICIs) remain unclear. We aimed to identify potential biomarkers of irTDs and reveal the association between irTDs and the clinical outcomes in patients with NSCLC treated with ICIs.

Methods: We conducted a retrospective study on 126 patients with NSCLC, who were treated with pembrolizumab, sintilimab, atezolizumab, or camrelizumab, as first-line therapy, at the First Affiliated Hospital, College of Medicine, Zhejiang University, between July 2019 and February 2023. Anti-thyroid antibodies (ATAs), thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TGAb), serum interleukin-6 (IL-6), thyroid ultrasonography, overall survival (OS), and progression-free survival (PFS) were the main indicators.

Results: Most (92.9%) irTD cases occurred no later than one year after ICIs initiation. Patients with irTDs had higher positive rates for ATAs and TPOAb [33.3% *vs.* 1.3%, and 30.3% *vs.* 1.3%, both $P < 0.01$, odds ratio (OR) = 39.81, and OR = 35.46, respectively]. Irregular echo pattern and diffuse changes were more common in patients with irTDs (70.7% *vs.* 47.2%, and 19.5% *vs.* 1.4%, $P < 0.05$ and $P < 0.01$, OR = 2.70, and OR = 17.21, respectively). OS and PFS were similar in patients with and without irTDs ($P > 0.05$).

Conclusions: The ATAs, TPOAb, and abnormal thyroid ultrasonographic findings (irregular echo patterns and diffuse changes) are potential biomarkers of irTDs. Patients with NSCLC treated with ICIs (pembrolizumab, sintilimab, atezolizumab, and camrelizumab) who developed irTDs had no advantage in terms of clinical outcomes compared to euthyroid patients.

Keywords: Programmed death 1 antibodies; anti-thyroid antibodies (ATAs); thyroid peroxidase antibody (TPOAb); immune checkpoint inhibitors (ICIs); abnormal thyroid ultrasonographic results

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Introduction

Background

The clinical application of immune checkpoint inhibitors (ICIs) represents a paradigm shift in the management of malignancies. Immune checkpoints regulate the immune activity, provide immune self-tolerance, and establish immune homeostasis. Cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), and its ligand (PD-L1) are among the most popular molecular targets in self-tolerance signaling pathways. They allow tumor cells to escape the immune system (1-3). Monoclonal inhibitors of CTLA-4 and PD-(L)1 have been reported to be associated with superior survival in malignancies, including non-small cell lung cancer (NSCLC) (4-8). However, immunotherapy-induced organ dysfunction, termed immune-related adverse events (irAEs), has been frequently recorded in clinical trials (9). IrAEs are commonly mild, but life-threatening in some circumstances, and have drawn widespread attention in clinical practice.

Rationale and knowledge gap

Immune-related thyroid dysfunction (irTD) is one of the most common irAEs, with an incidence of approximately 8% (9,10). Owing to the different definitions of irTDs

and the characteristics of asymptomatic manifestations, the incidence varied in different studies. However, the mechanisms underlying irTDs have not yet been elucidated. Anti-thyroid antibodies (ATAs) have been reported the possibility for irTDs prediction (11-14), but no consensus has been reached. Meanwhile, patients with an irregular echo pattern of the thyroid (14) and/or elevated thyroid-stimulating hormone (TSH) (15) levels at baseline are prone to develop irTDs. However, the impact of irTDs on the clinical outcomes of patients with NSCLC remains unclear. Better overall survival (OS) and/or progression-free survival (PFS) in malignancies have been described in some research (16-20), while no influence has been reported (21,22).

Objective

Our research was designed to improve the understanding of irTDs, including potential predictive biomarkers of irTDs and the link between irTDs and clinical outcomes of patients with NSCLC. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1092/rc>).

Methods

Patients

We conducted a retrospective study on patients with NSCLC who were treated with PD-(L)1 (pembrolizumab, sintilimab, atezolizumab, or camrelizumab) as the first-line therapy at the First Affiliated Hospital, College of Medicine, Zhejiang University, between July 2019 and February 2023. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the Independent Ethical Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No. 2023-0218). Informed consent was waived due to the retrospective nature of the study.

The inclusion criteria were as follows: (I) histologically confirmed NSCLC; (II) at least two courses of ICIs unless discontinued due to irTDs; and (III) at least two thyroid function detection tests after the initiation of ICIs. The exclusion criteria were as follows: (I) pre-existing thyroid diseases [hypothyroidism, subclinical hypothyroidism, hyperthyroidism, subclinical hyperthyroidism, and destructive thyroiditis (DH)] unless pre-existing subclinical thyroid diseases were aggravated due to ICIs; (II) fewer than three follow-ups; (III) absence of thyroid function at baseline; and (IV) fewer than two thyroid function detection

Highlight box

Key findings

- The development of immune-related thyroid dysfunctions (irTDs) had no impact on the survival of patients with non-small cell lung cancer (NSCLC).

What is known and what is new?

- The immune-related adverse events (irAEs) are major concern for clinical application of immune checkpoint inhibitors (ICIs) and has drawn wide research interest, with irTD as a common source.
- Firstly, it was found that thyroid peroxidase antibody (TPOAb), anti-thyroid antibodies (ATAs), and abnormal thyroid ultrasonography results were potential biomarkers of irTDs, which is consistent with previous studies. Secondly, no internal association was observed between irTD and the clinical outcomes of patients with NSCLC, which contracts with the previous literature conclusions.

What is the implication, and what should change now?

- For the irTD prediction, we suggest the usage of TPOAb, ATAs, and abnormal thyroid ultrasonography results as guidance.
- For the ICI treatment, we suggest that irTD may not be a main concern, although those with severe irTD still worth further attention and studies.

tests after the initiation of ICIs. Considering the potential influence of ICI types on the clinical outcomes of patients with NSCLC, the ICI types were balanced in group patients with irTD and group patients without irTD.

Assessment

Thyroid peroxidase antibody (TPOAb), serum interleukin-6 (IL-6), and thyroid ultrasonography data were available for most of the enrolled patients. Thyroglobulin antibodies (TGAb) were not detected in some patients. The normal reference ranges for TPOAb, TGAb, and serum IL-6 were 0–5.61 IU/mL, 0–4.11 IU/mL, and 0.10–2.90 $\mu\text{g/mL}$. The irTDs were classified as hypothyroidism, subclinical hypothyroidism (sub-hypo), hyperthyroidism, subclinical hyperthyroidism (sub-hyper), or DH (hypothyroidism secondary to transient hyperthyroidism). Two thyroid function detection tests were performed to confirm the diagnosis. The severity of irTDs was graded according to the Common Terminology Criteria for Adverse Events v5.0. The Age-adjusted Charlson Comorbidity Index (ACCI) was used to assess baseline comorbidities in patients with NSCLC. The smoking index (SI) was used to quantify smoking. PFS and OS were calculated according to the response evaluation criteria in solid tumors (RECIST) v1.1 criteria.

Statistical analysis

Statistical analyses were performed using the SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Numerical values with a normal distribution are expressed as the mean \pm standard deviation. The Mann-Whitney *U* test and Wilcoxon rank-sum test were used to compare continuous variables. The Kruskal-Wallis test, Fisher's exact test, and Chi-square test were used to compare categorical variables. Missing data were deleted and excluded from the statistical analysis. Kaplan-Meier curves were used to visualize and compare PFS and OS. All statistical tests were two-tailed, and the statistical significance level (*P*) was set at 0.05.

Results

Patient profiles

Out of a total of 569 patients screened out according to the inclusion and exclusion criteria, 84 euthyroid patients who were free from any irAEs and 42 patients presented

with irTDs were enrolled. The characteristics of the patients with and without irTDs are summarized in *Table 1*. The distribution of tumor node metastases and the ages of all patients are shown in *Figure 1*. Nine (7.1%) patients received ICIs monotherapy, four (44.4%) of whom developed irTDs. A total of 112 (88.9%) patients were administered adjunctive chemotherapy and 32 (25.4%) patients received adjunctive radiotherapy, of whom 36 (32.1%) and 14 (43.8%) developed irTDs, respectively. Twenty (15.9%) patients underwent surgery previously and switched to ICIs because of disease progression, among whom seven (35.0%) developed irTDs. The percentage of PD-L1 expression (PD-L1/%) and gene mutations were noted in 29 (23.0%) and 24 (19.0%) patients, respectively. Compared with euthyroid patients, irregular echo pattern and diffuse changes on thyroid ultrasonography were more common in patients with irTDs [70.7% vs. 47.2% and 19.5% vs. 1.4%, $P < 0.05$ and $P < 0.01$, odds ratio (OR) = 2.70, and OR = 17.21, respectively; *Table 2*]. There were no statistically significant differences in age, sex, SI, ACCI, chemotherapy, radiotherapy, surgery, PD-L1/%, ICI agents, or gene mutations between patients with irTDs and euthyroid patients.

irTD

The distribution and grades of irTDs are presented in *Table 3* and shown in *Figure 2*. Most (92.9%) patients developed irTDs no later than one-year after ICIs initiation, while 3 (7.1%) patients developed irTDs 62, 69, and 106 weeks after treatment initiation. Three (7.1%) patients with pre-existing sub-hypo showed disease aggravation after ICIs treatment. Twenty-three (54.8%) patients with irTDs required thyroid hormone replacement therapy, 1 (2.4%) required glucocorticoids, and 1 (2.4%) required metoprolol treatment. Transient discontinuity of ICIs was recorded in 8 (19.0%) patients, while ICIs therapies were discontinued permanently in 1 (2.4%) patient. Depressed TSH levels before the recognition of hypothyroidism or clinical hypothyroidism were observed in 4 (9.5%) patients. One patient (2.4%) recovered from irTDs, and 41 (97.6%) experienced irTDs until the end of the study. Eight patients (19.0%) developed other types of irAEs before and after irTDs.

Biomarkers

Baseline TPOAb, TGAb, and serum IL-6 levels were

Table 1 Characteristics of patients with NSCLC with or without irTDs

Characteristics	All (n=126)	irTDs (n=42)	Euthyroid (n=84)	P value
Age, years, mean ± SD	64.2±9.2	63.5±9.6	64.5±9.0	0.563
Male	109	34	75	0.197
SI, pack-years, mean ± SD	613.6±648.4	645.5±665.0	598.0±643.8	0.635
ACCI				>0.99
0–2	60	20	40	
3–6	66	22	44	
ECOG PS				0.159
0–1	117	37	80	
2–5	9	5	4	
Adjunctive chemotherapy	112	36	76	0.423
Adjunctive radiotherapy	32	14	18	0.148
Surgery previously	20	7	13	0.863
Thyroid ultrasonography				
Irregular echo pattern	62	28	34	0.030*
Diffuse change	9	8	1	0.001**
NA	12	1	11	
PD-L1/%				0.900
<1%	10	2	8	
1–49%	11	6	5	
≥50%	8	1	7	
NA	97	33	64	
ICI agents				>0.99
Pembrolizumab	54	18	36	
Sintilimab	36	12	24	
Atezolizumab	21	7	14	
Camrelizumab	15	5	10	
NSCLC histological subtypes				>0.99
Squamous carcinoma	69	23	46	
Adenocarcinoma	54	18	36	
Others	3	1	2	
Gene mutations				0.680
KRAS [†]	14	4	10	
EGFR	2	1	1	
RET fusion	3	1	2	
Others	5	3	2	
NA	61	21	40	

*, P<0.05; **, P<0.01. †, four patients with irTDs and nine patients without irTDs had the mutation in KRAS exon 2, one patient had the mutation in KRAS exon 4. NSCLC, non-small cell lung cancer; irTD, immune-related thyroid dysfunction; SD, standard deviation; SI, smoking index; ACCI, Age-adjusted Charlson Comorbidity Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status scale; NA, not available; PD-L1, programmed cell death-ligand 1; ICI, immune checkpoint inhibitor; KRAS, Kirsten rat sarcoma viral oncogene homolog; EGFR, epidermal growth factor receptor; RET, REarranged during Transfection.

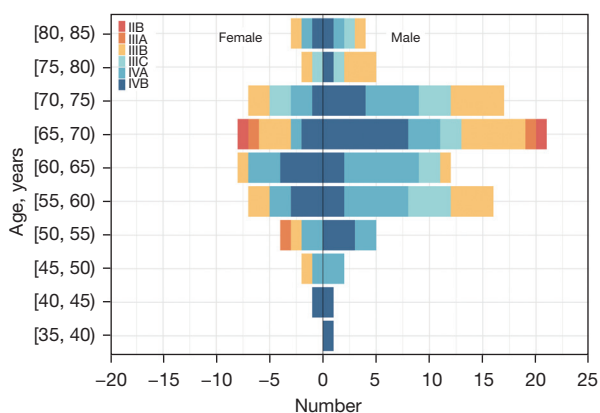


Figure 1 Distribution of tumor node metastases and age of all patients.

Table 2 Potential biomarkers of irTDs

Variables	OR	95% CI	P value
ATAs	39.81	4.86–326.19	<0.001**
TPOAb	35.46	4.30–292.26	<0.001**
TGAb	1.43	0.95–2.14	0.068
Irregular echo pattern	2.70	1.19–6.11	0.016*
Diffuse change	17.21	2.07–143.32	0.001**

*, $P < 0.05$; **, $P < 0.01$. irTD, immune-related thyroid dysfunction; OR, odds ratio; CI, confidence interval; ATAs, anti-thyroid antibodies; TPOAb, thyroid peroxidase antibody; TGAb, thyroglobulin antibody.

available for 112 (88.9%), 23 (18.3%), and 64 (50.8%) patients, respectively. Among the patients with irTDs, TPOAb, TGAb, and serum IL-6 levels at the time of irTDs were available for 34 (81.0%), 14 (33.3%), and 33 (78.6%) patients, respectively. The mean baseline TPOAb values were 57.04 and 0.92 IU/mL in patients with irTDs and euthyroid patients ($P < 0.05$; shown in *Figure 3A*). There were no statistical differences in the mean of TGAb and serum IL-6 at baseline between patients with irTDs and euthyroid patients (59.80 vs. 1.40 IU/mL, 26.24 vs. 46.96 pg/mL, $P > 0.05$; shown in *Figure 3B, 3C*). The positive rates of TPOAb and ATAs in patients with irTDs significantly differed from those in euthyroid patients (30.3% vs. 1.3%, 33.3% vs. 1.3%, OR = 35.46, and OR = 39.81, respectively; both $P < 0.01$; *Table 2*), whereas TGAb showed no difference (30.0% vs. 0%, $P = 0.068$). Elevated TPOAb at the time of irTDs was observed compared with the baseline (154.95 vs. 57.04 IU/mL, $P < 0.01$), while TGAb and IL-6 showed no

statistical differences (shown in *Figure 3*).

Survival

The PFS and OS were similar in patients with irTDs and euthyroid patients (10.96±6.94 vs. 9.70±6.45 months, 17.59±8.20 vs. 16.97±9.21 months, $P > 0.05$; shown in *Figure 4*). There were no differences in the PFS in ATAs-positive and ATAs-negative, TPOAb-positive and TPOAb-negative, and TGAb-positive and TGAb-negative patients (11.18±7.81 vs. 10.08±6.72 months, 11.58±8.07 vs. 10.07±6.73 months, 5.39±2.19 vs. 12.07±8.89 months, $P > 0.05$; shown in *Figures 5-7*). There were no differences in the OS in ATAs-positive and ATAs-negative, TPOAb-positive and TPOAb-negative, and TGAb-positive and TGAb-negative patients (19.10±8.89 vs. 17.33±8.90 months, 19.19±9.32 vs. 17.21±8.81 months, 10.64±7.60 vs. 22.54±10.26 months, $P > 0.05$; *Figures 5-7*). The PFS and OS of patients with irTDs grades one to three were similar (11.86±8.68 vs. 10.77±5.83 vs. 2.47 months, 19.81±10.08 vs. 16.77±6.63 vs. 5.67 months, $P > 0.05$).

Discussion

Key findings

Even though the paramount benefits derived from ICIs in patients with NSCLC have been extensively proven, irAEs can be life-threatening and need to be recognized as early as possible. The impact of irTDs on the clinical outcomes of patients with NSCLC and the potential biomarkers of irTDs remain unclear. Our study found that TPOAb, ATAs, and abnormal thyroid ultrasonography findings (irregular echo patterns and diffuse changes) are potential biomarkers of irTDs. There was no internal association between these potential biomarkers and the clinical outcomes of patients with NSCLC. The development of irTDs had no impact on the survival of patients with NSCLC.

Strengths and limitations

A retrospective study was conducted, on 126 NSCLC patients who were treated with pembrolizumab, sintilimab, atezolizumab, or camrelizumab as first-line therapy, at the First Affiliated Hospital, College of Medicine, Zhejiang University, between July 2019 and February 2023. ATAs, TPOAb, TGAb, serum IL-6, thyroid ultrasonography, OS, and PFS were the used as main indicators.

Table 3 irTDs in patients receiving ICIs therapy

ICI agent	All (n=42)	Hypothyroidism (n=21)		Hyperthyroidism (n=7)		DH (n=14)
		All	Overt	All	Overt	
Pembrolizumab	18	8	6	5	3	5
Sintilimab	12	7	4	1	1	4
Atezolizumab	7	3	2	1	1	3
Camrelizumab	5	3	1	0	0	2

irTD, immune-related thyroid dysfunction; ICI, immune checkpoint inhibitor; DH, destructive thyroiditis.

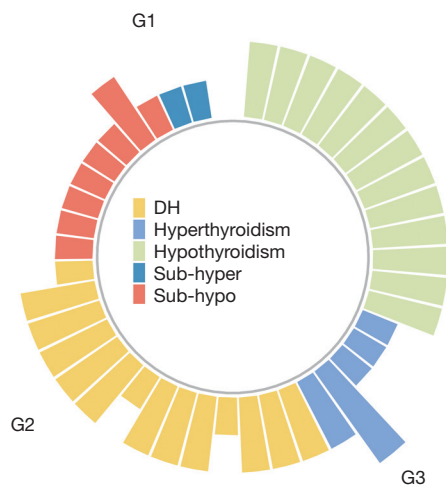


Figure 2 irTDs grades. DH, destructive thyroiditis; Sub-hyper, subclinical hyperthyroidism; Sub-hypo, subclinical hypothyroidism; G, grade; irTD, immune-related thyroid dysfunction.

Our study had some limitations. First, TGAb and serum IL-6 were not available in some patients. Second, the retrospective study design had its own limitations. Finally, more reported potential biomarkers were not included. Prospective randomized controlled trials are required in the future.

Comparison with similar researches and explanations of findings

The incidence of irTD was 7.4% in our study, which was close to the incidence reported previously (9,14). Most irTD cases developed no later than one-year after ICIs initiation. However, a small minority of patients suffered from irTDs after one-year duration of ICIs treatment. The onset time of irTDs we found was comparable to the former research (23). The irTDs grades were usually 1–2 similar to previous

research (24,25). No impact on ICIs treatment was believed to be caused by irTDs in a study conducted by Osorio *et al.* (16). However, transient and permanent discontinuities due to irTDs were recorded in our study. Only one patient achieved complete recovery from irTDs. Thus, we confirmed that irTDs were for the most part commonly irreversible (26). Hypothyroidism and DH were the most common irTDs. Surprisingly, decreased TSH levels were recorded before hypothyroidism or clinical hypothyroidism in some patients, indicating that an unrecognized and short hyperthyroidism phase may exist, and that the incidence of DH may be higher.

A prospective study conducted by Osorio *et al.*, of irTDs in patients with NSCLC receiving pembrolizumab showed an association between ATAs at baseline and irTDs (16). Positive TPOAb and/or TGAb levels have been reported as potential irTDs biomarkers in former studies (11,27–30). Similarly, we considered positive TPOAb and ATAs as potential biomarkers indicating a higher likelihood of irTDs. The significantly elevated TPOAb levels at the time of irTDs may be associated with the mechanism which have not yet been elucidated. In addition, abnormal thyroid ultrasonography findings, including irregular echo patterns and diffuse changes, were significantly more common in patients with irTDs than in euthyroid patients, suggesting the predictive value of irTDs in abnormal thyroid ultrasonography. Serum IL-6 has been reported as a potential biomarker of irAE (31). In contrast, a study conducted by Kurimoto *et al.* showed no association with irTDs (11). We recorded a similar situation for serum IL-6 levels. Considering the limited sample size of serum IL-6 and TGAb, we tentatively propose the tiny possibility of serum IL-6 and TGAb as potential biomarkers.

However, the impact of irTDs on the clinical outcomes of patients with NSCLC remains unclear. Skin and endocrine adverse events associated with better survival in patients

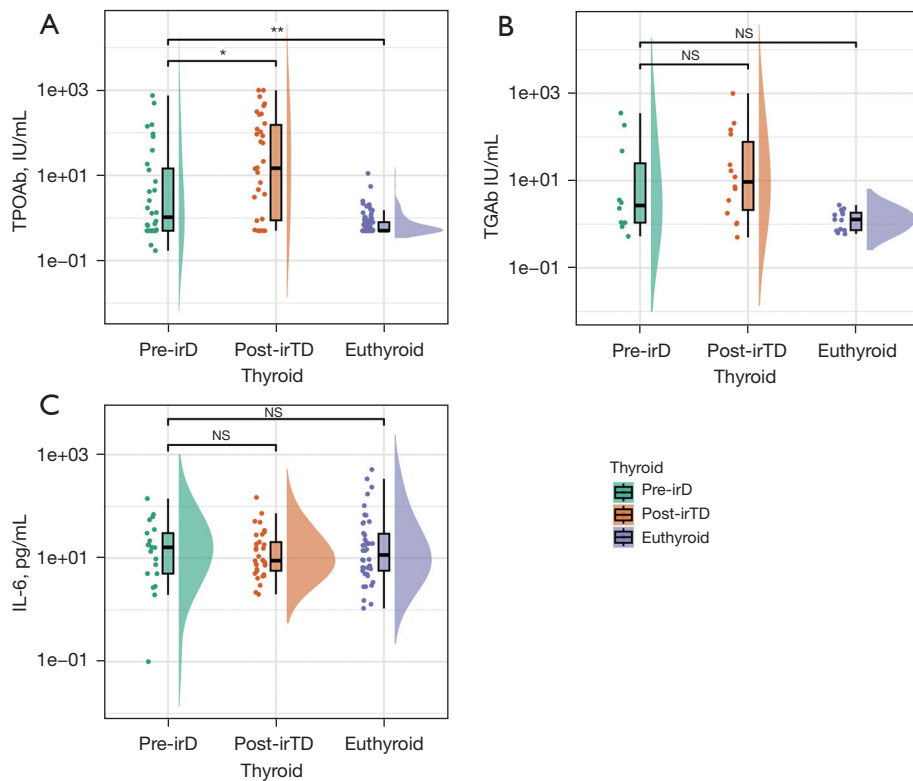


Figure 3 TPOAb (A), TGAb (B), and serum IL-6 (C) levels at baseline (pre-irTD and euthyroid) and the time of irTDs (post-irTD) in patients with irTDs and euthyroid patients. *, P<0.05; **, P<0.01. NS, Not significant (P>0.05); TPOAb, thyroid peroxidase antibody; TGAb, thyroglobulin antibody; IL-6, interleukin-6; irTD, immune-related thyroid dysfunction.

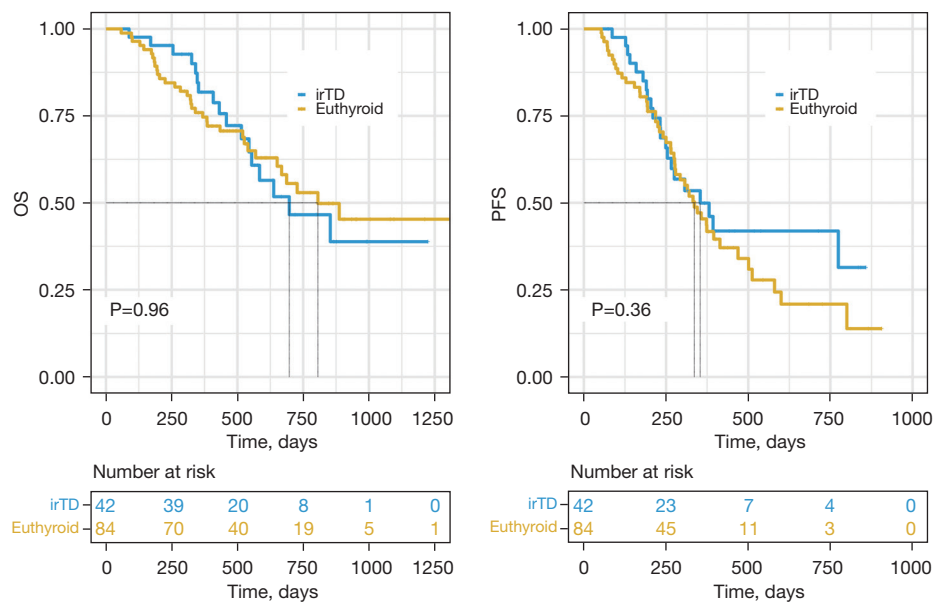


Figure 4 OS and PFS in patients with irTDs and euthyroid patients. OS, overall survival; PFS, progression-free survival; irTD, immune-related thyroid dysfunction.

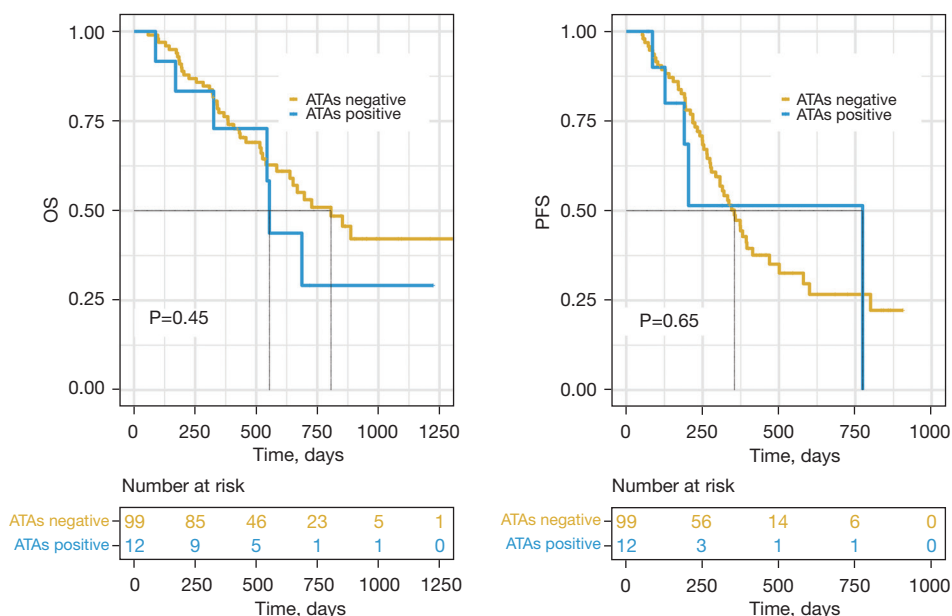


Figure 5 OS and PFS in ATAs-positive and ATAs-negative patients. OS, overall survival; PFS, progression-free survival; ATAs, anti-thyroid antibodies.

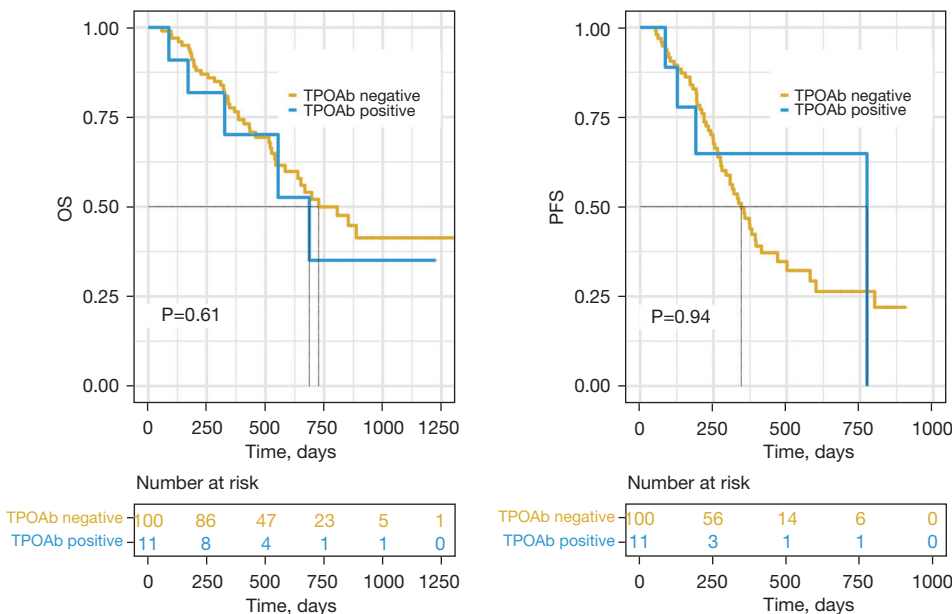


Figure 6 OS and PFS in TPOAb-positive and TPOAb-negative patients. OS, overall survival; PFS, progression-free survival; TPOAb, thyroid peroxidase antibody.

with NSCLC have been identified by Zhao *et al.* (32). Among patients with NSCLC, renal cell carcinoma, and metastatic melanoma who received nivolumab or pembrolizumab, those with overt irTDs had better OS

and PFS (19). Patients with higher ATAs levels showed better survival than those with lower ATAs levels in this study. Similarly, favorable OS and PFS have been reported in patients with irTDs and NSCLC (18). In contrast,

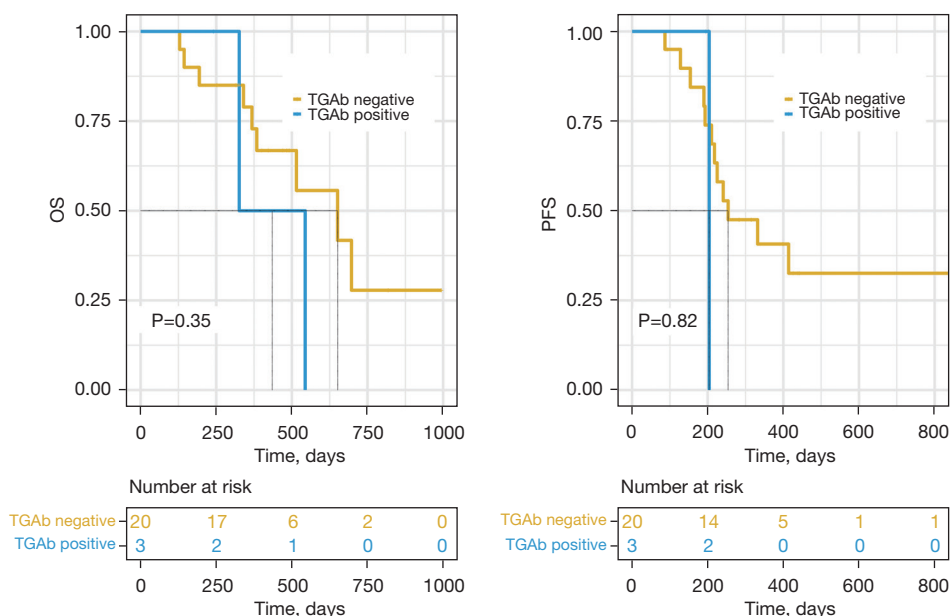


Figure 7 OS and PFS in TGAb-positive and TGAb-negative patients. OS, overall survival; PFS, progression-free survival; TGAb, thyroglobulin antibody.

irTDs were considered without better OS and (or) PFS in the patients with NSCLC in a few studies (21,22). No statistically significant difference was observed in the OS and PFS between patients with irTDs and euthyroid patients in our study, suggesting that irTDs had no obvious impact on the clinical outcomes of patients with NSCLC treated with ICIs. The same results were found for positive ATAs, TPOAb, and TGAb, which were in close proximity to those of a previous study (33).

Implications and actions needed

Thus, our study has two major suggestions for clinical practice. For the irTD prediction, we suggest the usage of TPOAb, ATAs, and abnormal thyroid ultrasonography results as guidance. For the ICI treatment, we suggest that irTD may not be a main concern, although those with severe irTD still worth further attention and studies.

Conclusions

The incidence of irTD induced by ICIs (pembrolizumab, sintilimab, atezolizumab, or camrelizumab) was 7.4%. irTD is prone to occur no later than 1-year after ICIs initiation. Discontinuity of ICIs may be required because of irTDs. We confirmed that ATAs, TPOAb, irregular echo patterns,

and diffuse changes on thyroid ultrasonography could be potential biomarkers for predicting irTDs. Patients with NSCLC treated with ICIs (pembrolizumab, sintilimab, atezolizumab, or camrelizumab) who developed irTDs had no advantages in terms of clinical outcomes compared with euthyroid patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1092/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the Independent Ethical Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (No. 2023-0218). Informed consent was waived due to the retrospective nature of the study.

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