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Risk factors of immune-related endocrine toxicities in non-small cell lung cancer patients treated with pembrolizumab and its impact on patient outcomes: a multicenter retrospective study

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Abstract

Background Pembrolizumab has been approved as a first-line treatment for non-small cell lung cancer (NSCLC) patients. However, a percentage of patients discontinue immunotherapy due to immune-related adverse events (irAE). Among these events, immune-related endocrine toxicities (E-irAE) represents the most common form, though their etiology, risk factors, and impact on patient outcomes remain poorly understood.

Materials and methods This retrospective cohort study was conducted across 5 multiple centers to investigate the outcomes of NSCLC patients who received pembrolizumab treatment between October 1, 2019, and September 30, 2023. E-irAE can occur on the thyroid, pituitary, adrenal glands, pancreas, and parathyroid. So thyroid function, adrenocorticotropic hormone, cortisol, sex hormone and glycaemia were measured at baseline and at regular intervals after the initiation of pembrolizumab treatment.

Results Our study included a total of 380 NSCLC patients treated with pembrolizumab, 114 patients (30.00%) developed E-irAE. Among them, 107 patients (93.86%) developed immune-related thyroid dysfunction (irTD) (5 cases of combined immune-related hypophysitis (IH)), 4 patients (3.51%) only developed IH, and 3 patients (2.63%) developed type 1 diabetes mellitus. IrTD was found to be independently associated only with monocyte-to-lymphocyte ratio (MLR) (odds ratios (*OR*) = 0.060, 95% *CI* 0.000-0.375; $p = 0.015$) and anti-thyroglobulin antibody (TGAb) (*OR* = 31.898, 95% *CI* 1.516-671.367; $p = 0.026$). *Kaplan-Meier* Survival Analysis showed that the progression-free survival (PFS) was significant longer in stage IV NSCLC patients with irTD than in those who did not (44.72 weeks vs. 27.79 weeks; hazard ratio (*HR*) = 0.645, 95% *CI* 0.440–0.946; $p = 0.025$), particularly in the subgroup of subclinical

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hypothyroidism (*HR* = 0.567, 95% *CI* 0.324–0.994; *p* = 0.047). We also found that sex (*HR* = 0.493, 95% *CI* 0.291–0.834; *p* = 0.008) was identified as an independent factor associated with better PFS.

Conclusion E-irAE are recognized as prevalent common irAE with various phenotypic manifestations. Low MLR and positive TGAb at baseline have been identified as risk factors that increase the likelihood of developing irTD. Sex and the occurrence of irTD were independently associated with improved PFS.

Keywords Non-small cell lung cancer, Immunotherapy, Immune-related endocrine toxicities, Immune-related thyroid dysfunction, Pembrolizumab

Introduction

According to Global Cancer Statistics 2020 [1], lung cancer has the second highest prevalence and the highest mortality rate among malignant tumors. In China, lung cancer has the highest incidence and mortality rates among cancers [2]. The two major histologic subtypes are non-small cell lung cancer (NSCLC) as well as small-cell lung cancer, accounting for approximately 80–85% and 15–20% of cases, respectively. With an enhanced understanding of tumor mechanisms, immunotherapy has become a promising treatment for malignant cancers.

In contemporary clinical practice, various immune checkpoint inhibitors (ICIs) are used, including programmed death-1/programmed death ligand-1 (PD-1/PD-L1) inhibitors and cytotoxic T lymphocyte-associated antigen-4 inhibitors. Pembrolizumab, a humanized monoclonal antibody and one of the most common PD-1 inhibitors [3], has been approved by the Food and Drug Administration and the National Medical Products Administration for advanced NSCLC. Clinical trials such as KEYNOTE-010 [4], KEYNOTE-024 [5], and KEYNOTE-042 [6] have demonstrated that pembrolizumab has superior outcomes in terms of overall survival (OS) and progression-free survival (PFS) compared to chemotherapy. Furthermore, other clinical trials, including KEYNOTE-021 [7], KEYNOTE-189 [8], and KEYNOTE-407 [9] have shown that the combination of pembrolizumab and chemotherapy also results in prolonged OS and PFS in NSCLC patients.

With increased utilization and indications, immune-related adverse event (irAE) has attracted considerable attention due to their high incidence and lethality in severe cases. IrAE can occur in any organ or tissue, immune-related endocrine toxicities (E-irAE) were the most common form of irAE. Importantly, immune-related thyroid dysfunction (irTD) is the most common E-irAE, while immune-related hypophysitis (IH), immune-related diabetes mellitus (DM), immune-related primary adrenal insufficiency (PAI) and hypoparathyroidism occur less frequently. Several investigations have examined potential risk factors associated with the development of irTD, including gender, age, body mass index (BMI), and antibodies. However, there is still controversy regarding the factors that contribute to the development of irTD, as different studies have reached disparate conclusions. Additionally, the association between the occurrence of irTD and the prognosis is still controversial. Therefore, we conducted further research to explore the incidence of irTD, potential risk factors, and the correlation between irTD and PFS among NSCLC patients treated with pembrolizumab in real-world settings.

Materials and methods

Patients and study design

This retrospective study was approved by the local medical ethics committees in 5 centers. The study included patients who received pembrolizumab treatment between October 24, 2019, and September 30, 2023. Relevant clinicopathological characteristics were collected, including age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), BMI, neoplasm stage, histological type, PD-L1 expression by immunohistochemistry, prior treatment, and baseline peripheral blood parameters.

Since E-irAE mainly include irTD, IH, ICI-DM, ICI-PAI and immune-related hypoparathyroidism, and the prevalence of these disorders is very high, we monitored thyroid function tests (TFTs), thyroid autoantibodies, ACTH, cortisol, and sex hormone, including prolactine (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), progesterone (P), testosterone (T) at baseline and every two cycles during treatment. Glycaemia and glycosylated hemoglobin were performed at baseline and every treatment cycle, if a patient develops hyperglycemia, we would evaluate pancreatic insulin reserve determined by C-peptide levels and diabetes related antibody (Ab) (glutamic acid decarboxylase anti-GAD-, insulin Ab-Anti-IA2- and islet cell Ab-ICA-). The diagnosis of IH was supported radiographically with an MRI of the pituitary gland.

The inclusion criteria included: (1) patients with pathologically and/or cytologically confirmed NSCLC; (2) patients with the administration of at least two doses of pembrolizumab, and a minimum of two measurements of tests following the initiation of treatment; (3) patients without endocrine-related disease before starting ICI therapy; Patients were excluded: (1) patients with endocrine malignancies or metastases; (2) patients had

previous treatment of any other ICIs; (3) patients with endocrine disease requiring medication at baseline; (4) patients had incomplete thyroid function assessment at baseline.

Definitions

IrTD refers to the identification of new-onset thyroid dysfunction subsequent to immunotherapy, excluding other potential causes. It was categorized into four groups based on the biochemical pattern of thyroid dysfunction. Overt hypothyroidism (Oho) referred to a Thyroid-stimulating hormone (TSH) level above the upper limit of the normal reference range and falling between 10.0 μIU/mL, with FT4 level below the reference range. Subclinical hypothyroidism (Scho) was defined as a elevated TSH level but FT4 level within the reference range. Overt hyperthyroidism (Ohe) referred to a TSH level below the lower reference range with FT4 level above the upper reference interval. Subclinical hyperthyroidism (Sche) was defined as a TSH level below the lower reference range with a normal FT4 level.

IH is a relatively rare irAE, characterized by a lack of specificity in clinical manifestations. Its diagnosis is presumptive, relying on clinical symptoms (e.g., headache and asthenia) and/or hyponatremia and/or at least one pituitary deficit and/or abnormal imaging [10]. DM typically occurs as rapid-onset hyperglycemia, and has a high risk of progressing to diabetic ketoacidosis in absence of prompt diagnosis and treatment [11]. The clinical manifestations of PAI often lack of specificity, it's typically characterized by low or relatively low plasma cortisol levels with elevated adrenocorticotrophic hormone (ACTH) [12]. Immune-related hypoparathyroidism can induce hypocalcemia, accompanied by nausea, vomiting, paresthesia, abdominal pain, and fatigue [12], it can be diagnosed with the level of parathyroid hormone.

The laboratory cut-offs utilized in hospitals were as follows: reference ranges of 0.35–4.94 mIU/L for TSH, 9.01–19.05 pmol/L for free thyroxine (FT4), 2.63–15.70 pmol/L for free triiodothyronine (FT3) levels, 0-4.11 IU/mL for thyroid peroxidase antibody (TPOAb), and 0-5.61 IU/mL for anti-thyroglobulin antibody (TGAb). Patients who initially experienced transient Ohe/Sche but subsequently developed hypothyroidism during the follow-up period were classified as the Oho/Scho group.

The time to onset of E-irAE was defined as the duration between the administration of the initial dose of ICI therapy and the first documented abnormality in the monitored hormones. PFS was determined as the time interval between the initiation of pembrolizumab and the first occurrence of disease progression or death.

Statistical analysis

Continuous quantitative variables with skewed distribution were compared using the *Wilcoxon test*, and summarized using the interquartile range (IQR). Categorical variables were compared using *Fisher's exact* test or the *Chi-square* test. Univariate logistic regression analysis was used to evaluate the baseline characteristics and biochemical associations with irTD. Factors with a p-value < 0.05 were included in a multivariate logistic regression model, and odds ratios (ORs) with their 95% confidence intervals (CIs) were presented. PFS for different groups was calculated using the *Kaplan-Meier* method, and the *log-rank* test was used for comparison between groups. Univariate and multivariate *Cox proportional hazard regression* models were used to estimate hazard ratios (HRs) and their 95% CIs. Prespecified subgroup analyses were conducted for patients with Oho, Scho, Ohe, and Sche, compared to patients without irTD. All statistical analyses were performed using IBM SPSS (version 25.0), and a p-value of < 0.05 was considered statistically significant. Figures were created using GraphPad Prism (version 9.5.1).

Results

Patient characteristics

A total of 479 patients with NSCLC who received pembrolizumab treatment in 5 medical centers were included. We excluded 99 patients from the analysis for various reasons, including 5 patients with a history of previous treatment with other ICIs, 41 patients with pre-existing endocrine disease prior to pembrolizumab therapy, 28 patients who lacked TFTs results, and 25 patients who received only a single dose of pembrolizumab. Therefore, a total of 380 patients were enrolled in our study (Fig. 1). The median age of the enrolled patients was 66.00 (59.00-70.25) years, with a majority of male participants (92.1%). Most patients had an ECOG PS of 0–1 (85.0%), and nearly half had a standardized BMI. The majority of NSCLC cases (62.1%) were classified as squamous cell carcinoma, with most patients diagnosed at stage IIIB + IIIC and stage IV (32.1% and 55.3%, respectively). PD-L1 expression data were available for 142 patients, with high expression (≥ 50%) observed in 13.4% of cases. The majority of patients (87.4%) received pembrolizumab as first-line therapy (Table 1).

Incidence, onset and outcomes of IrTD

Within the follow-up, irTD was observed in 107 (28.16%) of all patients. Among these cases, the most prevalent form of irTD was Sche (44.86%), followed by Scho (34.58%), Oho (16.82%), and Ohe (3.74%). The occurrence of irTD was typically observed within weeks to months after the initiation of pembrolizumab (Fig. 2). Interestingly, the onset of hyperthyroidism was earlier than

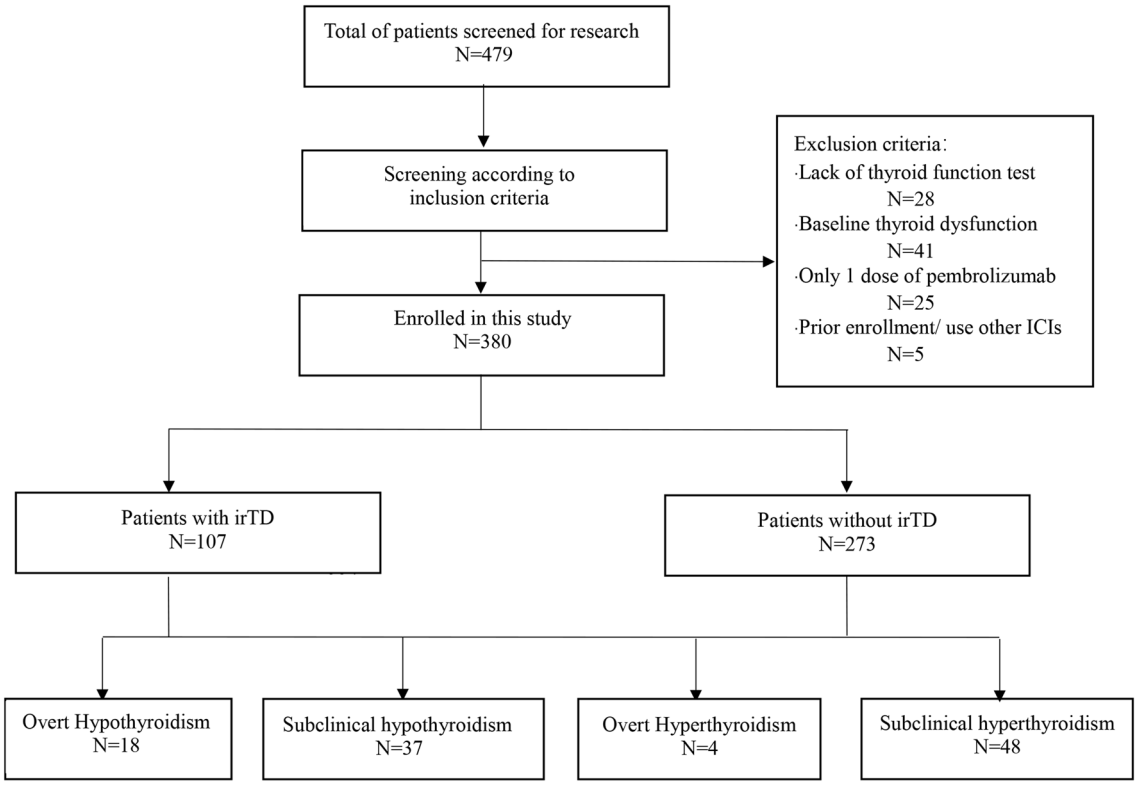

Fig. 1 Flowchart of patients selected

the onset of hypothyroidism (9.43 [6.86–19.71] weeks vs. 33.79 [17.68–69.47] weeks; $p < 0.001$). The time to Oho onset ranged from 7.43 to 75.57 weeks, for Scho it ranged from 3.29 to 203.29 weeks, for Ohe it ranged from 5.86 to 71.14 weeks, and for Sche it ranged from 2.14 to 86.86 weeks. The median time to Oho onset was 22.64 (15.54–27.57) weeks, while for Scho it was 34.86 (16.00–67.00) weeks, for Ohe it was 8.21 (6.39–25.18) weeks, and for Sche it was 9.79 (6.71–15.11) weeks. Among the 55 patients who presented with hypothyroidism, 25.45% experienced transient hyperthyroidism before the onset of hypothyroidism, with a median time of 8.29 (5.79–13.22) weeks. Notably, patients with Ohe (6/10) demonstrated a higher risk of developing subsequent hypothyroidism compared to those with Sche (5/53).

Overall, the outcomes of patients with irTD were favorable, with TSH levels returning to normal levels in 5 cases of Oho; while 19 cases of Scho, 2 cases of Ohe, and 34 cases of Sche also showed normalization of TSH levels. Regarding FT4 levels, 11 cases of Oho and 3 cases of Ohe achieved normalization. However, it should be noted that the majority of cases still exhibited abnormalities in autoantibodies. Permanent hypothyroidism requiring levothyroxine replacement therapy was more prevalent among patients with Oho (38.9%) compared to those with Scho (5.4%). Importantly, none of the patients discontinued their medication due to severe irTD.

Incidence, onset and outcomes of IH

Among the 380 patients, IH was the second common type of E-irAE (9 patients; 7.89%), the median time to IH onset was 42.57 (25.14–62.29) weeks. Most patients were squamous cell carcinoma (7 patients; 77.78%), with a mean age of 66.12 years and all of them had ACTH deficiency. 5/9 patients had concurrent irTD, but only case 9 required replacement treatment with levothyroxine. All patients presented with fatigue, followed by headache (77.78%) as the second most common syndrome. Interestingly, case 3 exhibited increased urine output, while case 7 had low blood pressure. Notably, none of them had abnormal findings on pituitary MRI (Table 2).

All patients diagnosed with IH needed replacement treatment with glucocorticoids, and their outcomes were good, none of them required permanent discontinuation of medication due to severe IH. Specifically, all patients achieved normalization of ACTH levels, while only 3 cases demonstrated restoration of cortisol levels to within the normal range (Table 2).

Incidence, onset and outcomes of DM

There were 3 cases (2.63%) of newly developed DM during pembrolizumab treatment in our study, with a median onset time of 30.43 (20.64–34.93) weeks. Furthermore, their fasting blood glucose (FBG) level were found to be higher than 13.9 mmol/L, and C-peptide

Table 1 Clinical characteristics in NSCLC patients

Baseline characteristics	All patients (*n* = 380)	With irTD (*n* = 107)	Euthyroid (*n* = 273)	t/χ^2/Z	*p* value
Age (years)	66.00 (59.00-70.25)	66.00 (60.00–71.00)	64.00 (59.00–71.00)	1.398	0.162
Sex				0.055	0.815
Male	350(92.1)	98(91.6)	252(92.3)		
Female	30(7.9)	9(8.4)	21(7.7)		
ECOG PS(*n* = 234);				0.017	0.897
0–1	199(85.0)	59(85.5)	140(84.8)		
≥ 2	35(15.0)	10(14.5)	25(15.2)		
BMI				4.616	0.099
<18.5 kg/m^2	30(7.9)	5(4.7)	25(9.2)		
18.5–24 kg/m^2	221(58.2)	58(54.2)	163(59.7)		
≥ 24 kg/m^2	129(33.9)	44(41.1)	85(31.1)		
Histological features				0.017	0.898
Non-squamous cell carcinoma	144(37.9)	40(37.4)	104(38.1)		
Squamous cell carcinoma	236(62.1)	67(62.6)	169(61.9)		
Neoplasm stage				1.575	0.455
II/IIIA	48(12.6)	10(0.9)	38(2.9)		
IIIB/IIIC	122(32.1)	37(34.6)	85(31.1)		
IV	210(55.3)	60(56.1)	150(54.9)		
PD-L1 TPS(*n* = 142)				3.102	0.212
<1%	97 (68.3)	25(58.1)	72(72.7)		
1–49%	26(18.3)	11(25.6)	15(15.2)		
≥ 50%	19(13.4)	7(16.3)	12(12.1)		
Prior treatment or combination					
surgical history	64(16.8)	19(17.8)	45(16.5)	0.089	0.765
chemotherapy history	362(95.3)	102(95.3)	260(95.2)	0.001	0.971
radiotherapy history	38(10.0)	13(12.1)	25(9.2)	0.765	0.382
molecular targeted therapy	10(2.6)	2(1.9)	8(2.9)	0.338	0.561
Treatment Line				2.438	0.196
I	332(87.4)	89(83.2)	243(89.0)		
II	33(8.7)	12(11.2)	21(7.7)		
≥III	15(3.9)	6(5.6)	9(3.3)		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; BMI, body mass index. TPS, Tumor Proportion Score

levels were consistently below the normal range. Interestingly, their HbA1c levels were only slightly elevated above the normal range. All 3 cases exhibited fulminant type 1 diabetes, with case 3 experiencing the additional complication of diabetic ketoacidosis (DKA). Due to two cases being graded as Grade 3 and one case as Grade 4

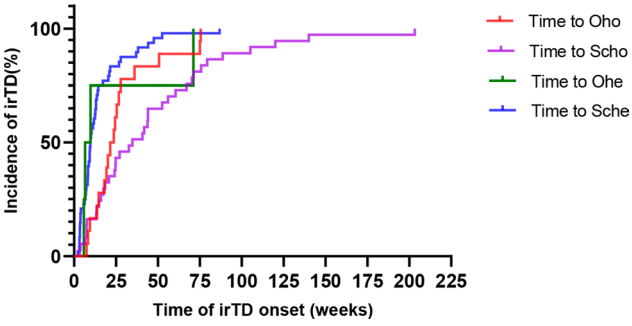

Fig. 2 Relationship between time of irTD onsets and incidence of irTD

(according to CTCAE 5.0), all three patients temporarily discontinued pembrolizumab treatment and received symptomatic management with insulin and oral hypoglycemic agents. However, pembrolizumab treatment was restored in all cases once they achieved stable blood glucose control (Table 3).

Clinical features and biomarkers

No statistically significant differences were observed between the irTD group and euthyroid group in terms of age, sex, ECOG PS, BMI, histological features, neoplasm stage, PD-L1 TPS, treatment line, and prior treatment. Analysis of baseline peripheral blood results revealed several correlations with the development of irTD. Specifically, monocyte-to-lymphocyte ratio (MLR) (IQR = 0.36[0.26–0.51]; Z = 2.255, $p = 0.024$), FT3 levels (IQR = 4.12[3.75–4.53]; Z = 1.975, $p = 0.048$), positive expressions of TPOAb at baseline (positive: 11/76 vs. 8/173; $x^2 = 7.286$, $p = 0.007$) and TGAb at baseline (positive: 5/19 vs. 2/46; $x^2 = 4.660$, $p = 0.031$) were found to be statistically associated with the incidence of irTD (Table 4).

Previous studies have suggested that the occurrence of irTD may be associated with chemotherapy history, baseline TSH levels [13], gender [14], age and BMI [15]. In this study, the *Wilcoxon test* and *Chi-square test* analyses revealed statistically significant differences in baseline MLR, FT3, TPOAb, and TGAb at baseline between groups ($p < 0.05$), and therefore the presence or absence of a history of chemotherapy, baseline MLR, TSH, FT3, FT4, gender, age, BMI, TPOAb, and TGAb were finally included in the binary logistic regression analysis. The analysis demonstrated that was only MLR (*OR* = 0.060, 95% *CI* 0.000-0.375; $p = 0.015$) and TGAb at baseline (*OR* = 31.898, 95% *CI* 1.516-671.367; $p = 0.026$) were associated with the occurrence of irTD (Fig. 3).

Although there was no statistical significance when comparing the irTD and euthyroid groups, it is worth noting that TSH levels exhibited a significant correlation with the onset of irTD when comparing the different clinical phenotypes separately. Specifically, in the Oho group, TSH levels showed a positive correlation (*OR* = 1.874,

Table 2 Patients with immune-related hypophysitis during follow up

Case	Age	Sex	Histological features	Occurrence time (weeks)	Pituitary hormone deficiency	Syndrome	Pituitary MRI	Prognosis
1	66	M	squamous cell carcinoma	25.14	ACTH FSH Cortisol	Fatigue	Negative	ACTH recovery
2	59	M	squamous cell carcinoma	67.43	ACTH Cortisol	Headache Fatigue	Negative	ACTH recovery
3	65	M	squamous cell carcinoma	42.57	ACTH FSH Cortisol	Headache Fatigue increased urine output	N. A	ACTH recovery
4	78	M	squamous cell carcinoma	62.29	ACTH TSH Cortisol	Fatigue	N. A	recovery
5	67	M	non-squamous cell carcinoma	80.86	ACTH TSH FSH LH Cortisol	Headache Fatigue	Negative	ACTH, TSH, cortisol and FSH recovery
6	73	M	squamous cell carcinoma	17.86	ACTH TSH FSH Cortisol	Headache Fatigue	Negative	ACTH recovery
7	56	M	squamous cell carcinoma	24.86	ACTH TSH Cortisol	Headache Fatigue Low blood pressure	N. A	ACTH recovery
8	70	M	squamous cell carcinoma	44.00	ACTH FSH LH PRL Cortisol	Headache Fatigue	Negative	recovery
9	61	F	Non-squamous cell carcinoma	37.86	ACTH TSH cortisol	Headache Fatigue	Negative	ACTH recovery

Abbreviations: M, male; F, female; ACTH, adrenocorticotrophic hormone; TSH, thyroid-stimulating hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactine; N.A, not available data

Table 3 Patients with immune-related diabetes mellitus during follow up

Case	Age	Sex	Occurrence time (weeks)	Syndrome	Manife-stations	FBG (mmol/L)	HbA1c (%)	C-peptide (pmol/L)	antibody	prognosis
1	52	M	10.86	Polyuria Polydipsia Polyphagia Weight loss	T1DM	20.07	8.9	2.71	N. A	Continue ICI glycemic control
2	69	M	39.43	Polyuria Polyphagia	T1DM	15.59	7.6	< 0.01	GAD (+) IA2 (-)	Continue ICI glycemic control
3	70	M	30.43	Fatigue Polyuria Polydipsia Polyphagia Nausea	DKA	74.53	7.1	< 0.01	GAD (-) IA2 (-) ICA (-)	Continue ICI glycemic control

Abbreviations: T1DM, Type 1 diabetes mellitus; DKA, Diabetic Ketoacidosis; FBG, Fasting Blood Glucose; HbA1c, Glycosylated Hemoglobin A1c; GAD, glutamic acid decarboxylase; IA2, insulin Antibody; ICA, islet cell antibody

95% *CI* 1.094–3.208, $p = 0.022$), while in the Scho group, a similar positive correlation was observed ($OR = 2.214$, 95% *CI* 1.522–3.219, $p < 0.001$). In contrast, the Sche group demonstrated a negative correlation between TSH levels and irTD ($OR = 0.186$, 95% *CI* 0.090–0.386, $p < 0.001$). Moreover, there was no statistically significant difference in FT4 levels and treatment lines between the groups (Table 5).

Outcomes survival

Kaplan-Meier Survival Analysis found that stage IV NSCLC patients who developed irTD during

Table 4 Baseline peripheral blood results in NSCLC patients

Baseline peripheral blood results; median (IQR)	irTD (*n* = 107)	Euthyroid (*n* = 273)	$t/x^2/Z$	*p* value
PLR	170.09 (128.53-237.38)	184.76 (135.42-266.43)	1.627	0.104
NLR	3.54 (2.30–5.06)	3.56 (2.33–5.43)	1.525	0.127
MLR	0.36 (0.26–0.51)	0.40 (0.29–0.55)	2.255	0.024
CRP	8.40 (2.385–31.85)	8.55 (3.00-31.60)	0.391	0.696
LDH	190.00 (173.00-214.50)	191.00 (166.00-236.00)	0.396	0.692
CD3 + T %	69.20 (63.03–74.90)	70.20 (63.95–75.98)	0.873	0.383
CD4 + T %	40.23 (31.59–46.10)	38.81 (32.40–45.90)	0.133	0.894
CD8 + T %	24.63 (20.20–31.20)	25.45 (20.20-32.11)	0.462	0.644
CD4 + T/ CD8 + T %	1.54 (1.15–2.04)	1.54 (1.07–2.03)	0.421	0.673
CD19 B %	10.60 (7.20–13.90)	9.23 (6.30–13.20)	1.087	0.277
NK CD16/CD56%	20.10 (12.19–28.20)	18.80 (11.80–24.50)	0.831	0.406
Baseline TSH	1.33 (0.78–2.27)	1.35 (0.94–1.95)	0.426	0.670
Baseline FT3	4.12 (3.75–4.53)	3.99 (3.64–4.38)	1.975	0.048
Baseline FT4	12.86 (11.52-14.00)	13.03 (12.12–14.04)	1.541	0.123
Baseline TPOAb (*n* = 249); n (%)			7.286	0.007
Positive	11 (14.5)	8 (4.6)		
Negative	65 (85.5)	165 (95.4)		
Baseline TGAb (*n* = 65); n (%)			4.660	0.031
Positive	5 (26.3)	2 (4.3)		
Negative	14 (73.7)	44 (95.7)		
TPOAb after initiation of immunotherapy (*n* = 79); n (%)			0.000	> 0.999
Positive	1 (16.7)	16 (25.4)		
Negative	5 (83.3)	47 (74.6)		
TGAb after initiation of immunotherapy (*n* = 33); n (%)			0.220	0.639
Positive	1 (25.0)	14 (48.3)		
Negative	3 (75.0)	15 (51.7)		

Abbreviations: IQR, interquartile range; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; CRP, C-reactive protein; LDH, lactate dehydrogenase; TSH, Thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TPOAb, thyroid peroxidase antibody; TGAb, anti-thyroglobulin antibody

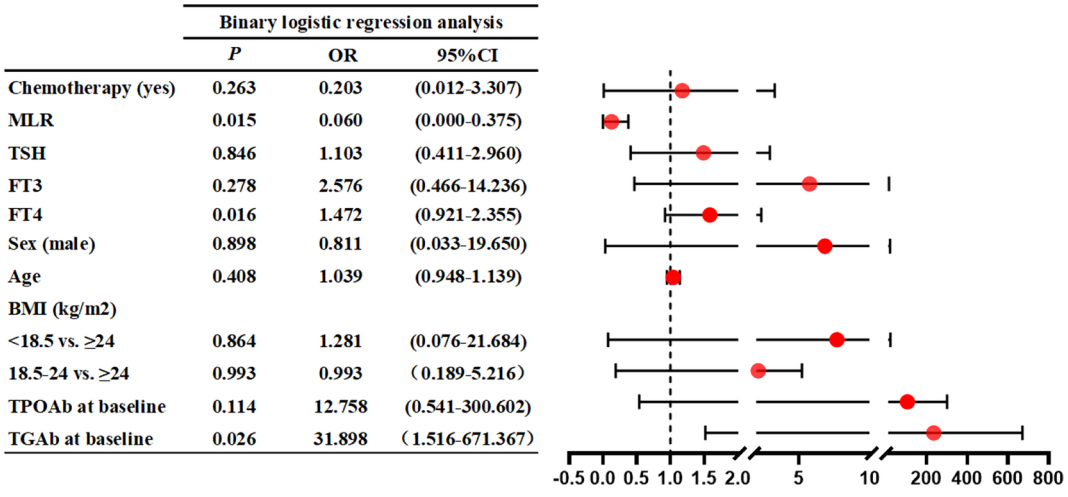

Fig. 3 Binary logistic regression analysis for independent risk factors of irTD onset

Table 5 Clinical and biochemical associations with patients with pembrolizumab associated different subtypes of IrTD during follow-up

Factors	irTD		Oho		Scho		Ohe		Sche	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
MLR	0.330 (0.130–0.840)	0.020	0.182 (0.019–1.766)	0.142	0.264 (0.055–1.262)	0.095	0.000 (NA-0.803)	0.045	0.441 (0.131-1.629)	0.185
TSH	1.148 (0.896–1.470)	0.275	1.874 (1.094–3.208)	0.022	2.214 (1.522–3.219)	< 0.001	0.525 (0.100-2.759)	0.447	0.186 (0.090-0.386)	< 0.001
FT4	0.873 (0.755–1.010)	0.067	0.860 (0.600-1.232)	0.411	0.845 (0.652–1.094)	0.200	0.921 (0.478–1.777)	0.807	0.966 (0.787-1.186)	0.742
Treatment	1.413 (0.903–2.209)	0.130								
I vs. ≥III			0.191 (0.033–1.086)	0.062	1.121 (0.127–9.869)	0.918	NA	NA	0.369 (0.084-1.629)	0.188
II vs. ≥III			1.759 (0.263–11.736)	0.560	3.549 (0.336–37.493)	0.292	NA	NA	NA	0.995

Abbreviations: MLR, monocyte-to-lymphocyte ratio; TSH, Thyroid-stimulating hormone; FT4, free thyroxine; irTD, immune-related thyroid dysfunction; Oho, overt hypothyroidism; Scho, subclinical hypothyroidism; Ohe, overt hyperthyroidism; Sche, subclinical hyperthyroidism; I, first-line therapy; II, second-line therapy; III, third-line therapy; NA, not available

immunotherapy had a longer PFS compared to those who remained euthyroid (44.72 weeks vs. 27.79 weeks; *HR* = 0.645, 95% *CI* 0.440–0.946; *p* = 0.025)Fig. 4A). However, the difference in PFS between stage IIIB/IIIC NSCLC patients who developed irTD during immunotherapy was not statistically significant compared to those who did not develop irTD (*HR* = 0.776, 95% *CI* 0.436–1.381; *p* = 0.387)Fig. 4C). To further explore the relationship between irTD and prognosis, we subdivided irTD into subclinical and overt categories. In subgroup comparisons, PFS was improved in the Scho group compared to the euthyroid group with statistical significance in stage IV NSCLC patients (*HR* = 0.567, 95% *CI* 0.324–0.994; *p* = 0.047), while no significant difference was observed between the other subtype groups and euthyroid group (Fig. 4B, 4D).

The results of the meta-analysis of Dall'Olio [16] et al. showed that immortal time bias had an real effect on PFS in patients. Therefore, we used 6 weeks as a time point, and patients who experienced death or progression within 6 weeks were included in the euthyroid group. As the result of univariate Cox regression analysis, only sex (*HR* = 1.995, 95% *CI* 1.192–3.340; *p* = 0.009) was found to be associated with PFS in patients with stage IV NSCLC in our study, but no correlation was found between age, ECOG, BMI, histological features, PD-L1 TPS, number of lines of treatment, and immortal time bias and PFS ($p>0.05$) (Table 6).

However, previous studies have shown that age, number of lines of treatment, and treatment history may all be associated with PFS in cancer patients [17], therefore we included all the above variables as covariates in the multivariate Cox regression analysis along with the occurrence of irTD, and found that sex (*HR* = 0.493, 95% *CI* 0.291–0.834; *p* = 0.008) and the occurrence of irTD (*HR* = 0.603, 95% *CI* 0.397–0.916, *p* = 0.018) were independent predictors of a favorable prognosis (Fig. 5).

Discussion

E-irAE is a common adverse event induced by PD-1 inhibitors, and severe cases can pose life-threatening risks. Pembrolizumab is one of the most commonly used PD-1 inhibitors, but there is limited research on the E-irAE relevant with it in the real world, data comes mainly from the clinical trials. Our study aims to investigate the incidence, onset and outcomes of E-irAE, identify risk factors associated with the development of irTD, and examine the potential association between irTD and better PFS in patients treated with pembrolizumab in a real-world clinical setting.

Several previous meta-analyses have shown that irTD and IH are the most common E-irAE, while DM, PAI and hypoparathyroidism are rare [18, 19]. Because of the small number of events, statistical inferences were made only

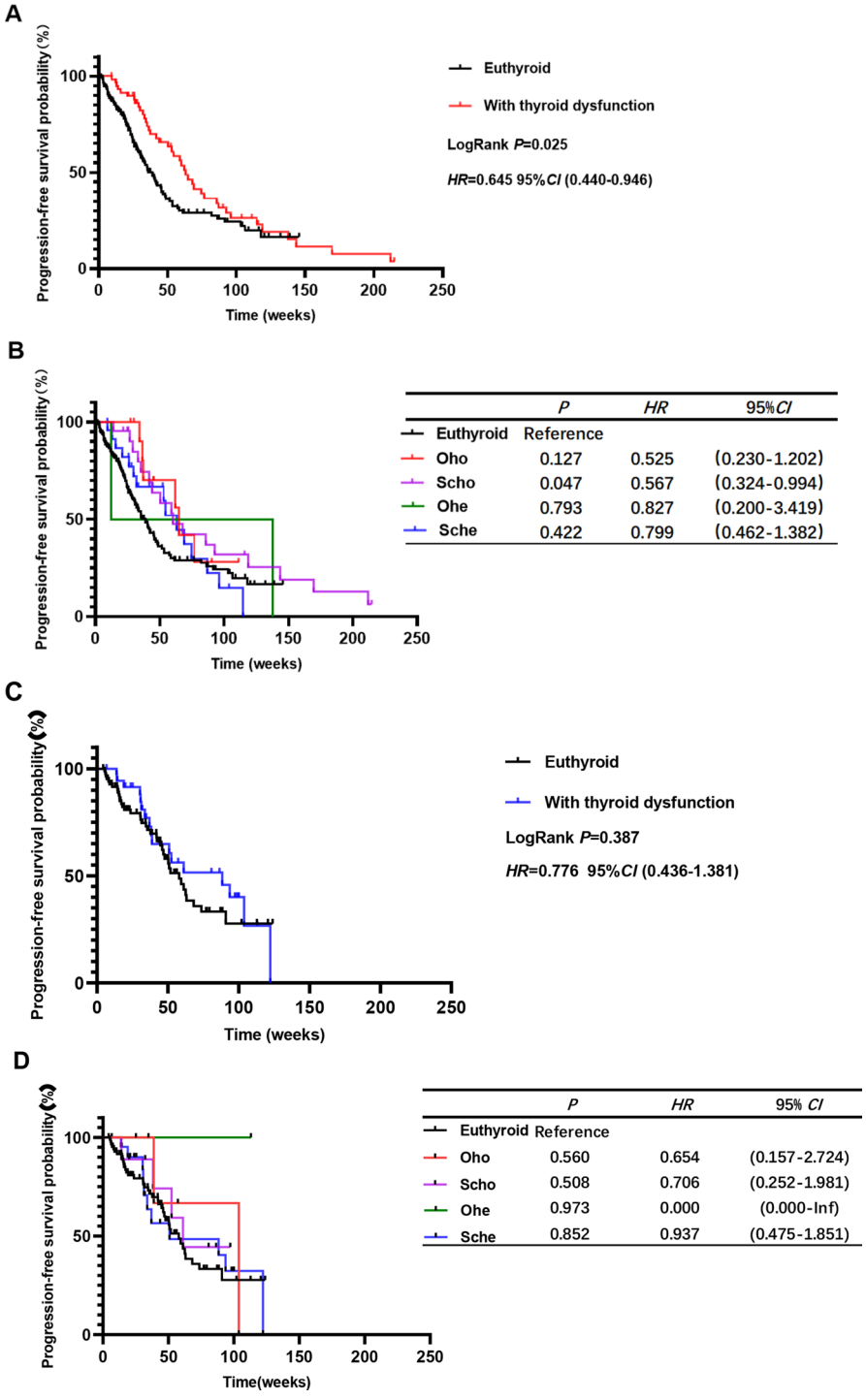

Fig. 4 *Kaplan-Meier* estimates of progression-free survival (PFS) in stage IV NSCLC patients with irTD after pembrolizumab therapy. (**A**) PFS in stage IV NSCLC patients with irTD relative the patients who remained euthyroid. (**B**) PFS in stage IV NSCLC patients with Oho, Scho, Ohe, and Sche compared to the patients who remained euthyroid. (**C**) PFS in stage IIIB/IIIC NSCLC patients with irTD was not significantly difference from the patients who remained euthyroid. (**D**) PFS in stage IIIB/IIIC NSCLC patients with Oho, Scho, Ohe, and Sche compared to the patients who remained euthyroid

for irTD and descriptive analyses were made for other types of E-irAE. Interestingly, in our cohort, although we only observed 2.36% of patients developed IH, the incidence was still higher than it in previous meta-analysis [19]. Additionally, 0.79% of patients developed DM and did not observe PAI or hypoparathyroidism.

The reported incidence of irTD ranges from 10.9 to 19.5%, hypothyroidism ranges from 7.9 to 12.1% and

Table 6 Univariate Cox regression analysis of independent prognostic factors of PFS for stage IV NSCLC patients

Baseline characteristics	HR	95% CI	*P*
Age	0.907	0.966–1.008	0.210
Sex (Male)	1.995	1.192–3.340	0.009
ECOG PS (0–1)	1.597	0.924–2.760	0.094
BMI			
<18.5 kg/m2 vs. 18.5–24 kg/m2	0.648	0.309–1.358	0.250
<18.5 kg/m2 vs. ≥ 24 kg/m2	0.762	0.358–1.621	0.480
Histological features (Non-squamous cell carcinoma)	1.396	0.984–1.980	0.061
PD-L1 TPS			
<1% vs. 1–49%	1.249	0.608–2.569	0.545
<1% vs. ≥50%	1.144	0.400-3.271	0.802
Prior treatment or combination			
surgical history	1.176	0.781–1.772	0.437
chemotherapy history	0.753	0.348–1.632	0.473
radiotherapy history	1.001	0.632–1.587	0.996
molecular targeted therapy	0.973	0.309–3.063	0.963
Treatment Line			
I vs. II	0.755	0.405–1.406	0.375
I vs.≥III	0.995	0.478–2.073	0.990

Abbreviations: ECOG, Eastern Cooperative Oncology Group; BMI, body mass index. TPS, Tumor Proportion Score

hyperthyroidism from 4.0–7.8% [4–9, 20]. In our study, 28.2% of NSCLC patients presented with irTD, with 14.5% manifesting hypothyroidism and 13.7% manifesting hyperthyroidism. The observed frequency of irTD was higher compared to that reported in prior clinical trials but similar to findings from earlier real-world investigations [21, 22]. The above findings indicate that the incidence of irTD in the real world may be underestimated. Moreover, irTD was categorized into four subtypes, with Sche being the most prevalent, followed by Scho, Oho, and Ohe. However, this result differs from previous studies [23, 24], which could be attributed to the inclusion of solely NSCLC patients in our study, whereas prior investigations encompassed diverse tumor types.

Hyperthyroidism typically manifests within a few weeks to 6 months after the initiation of ICIs and has a median onset time that precedes that of hypothyroidism. Consistent with this finding, our study also revealed a disparity in the median onset times of hyperthyroidism and hypothyroidism ($p < 0.001$). Further analysis using the *Wilcoxon test* showed a difference in the median time to irTD onset across different subgroups with statistical significance ($p = 0.001$), particularly between Sche group and either Oho group or Scho group ($p = 0.023$; $p < 0.001$, respectively). However, it is noteworthy that the median time to onset of irTD in our study exceeded that previously reported [25–31], possibly due to inadequate regular monitoring of thyroid function.

In our study, all patients with hyperthyroidism and the majority of those with hypothyroidism experienced self-limiting symptoms, indicating that the grading of irTD was generally mild, which was consistent with previous reports [5, 6, 8, 20, 32]. We also found that a higher proportion of patients in the Oho subgroup, compared to the Scho subgroup, required levothyroxine replacement therapy for permanent hypothyroidism (7/18 vs. 2/37).

Several articles have investigated clinical factors related to irTD, but none have demonstrated a definitive correlation. In our cohort, age, gender, and BMI did not emerge as risk factors for irTD, possibly due to differences in cancer types, potential data bias, and limited statistical power [14, 15, 23, 33], but similar to other reports on irTD in lung cancer patients treated with nivolumab [21, 22]. Although previous studies have indicated that a low neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) at baseline may be associated with the occurrence of irAEs [34, 35], we did not observe such correlations in our study. Additionally, we found a low MLR at baseline acted as an independent risk factor for irTD, specifically for Ohe. Our conclusions are similar to those of previous articles suggesting that elevated TSH levels at baseline could serve as a predictor of irTD [23, 36, 37]. However, it is worth noting that we did not find an association between Ohe and TSH levels in the

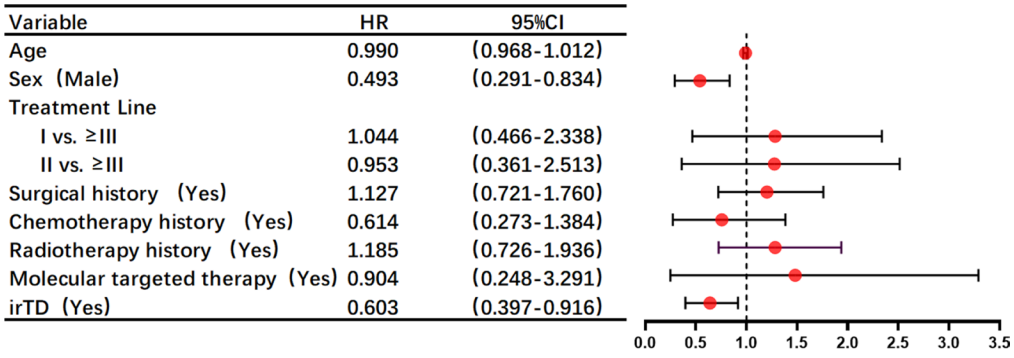

Fig. 5 Multivariate Cox regression analysis of independent prognostic factors of PFS for stage IV NSCLC patients

present study, which may be attributed to the insufficient sample size.

The relationship between baseline positivity of TPOAb, TGAb and the occurrence of irTD remains unclear. Previous researches have yielded conflicting findings regarding the potential impact of baseline TGAb and TPOAb positivity on the development of irTD [29, 38, 39], while others have found no correlation [40, 41]. Some studies have suggested that it is the presence of baseline TGAb, rather than TPOAb, that increases the risk of irTD [13, 36], while others have proposed that positive TGAb and TPOAb after ICIs therapy may serve as predictive factors [42, 43]. However, our results demonstrate a possible predictive role of baseline TGAb positivity in relation to irTD. It is hypothesized that irTD may be caused by an antibody-independent pathway or by an unidentified antibody [41].

Although several studies have shown a significant improvement in PFS among patients with irTD [23, 44, 45], there have been inconsistent findings reported in some studies [29]. This inconsistency could potentially be attributed to limited sample sizes. In our study, we confirmed these previous observations through Cox multivariate analysis, which revealed that irTD independently contributed to a prolonged PFS (Fig. 5). However, the underlying mechanisms remain unclear and require further investigation through large-scale studies. Moreover, we found that male patients with NSCLC was another independent protective factor associated with a longer PFS.

This study had some limitations that warrant discussion. Firstly, it is important to acknowledge that our research design was a retrospective study, which may introduce inherent biases, and our sample size may not have been sufficient for subgroup analysis in NSCLC patients with E-irAE. It is noteworthy that 350 of the 380 patients included in this study were male, accounting for 92.1%. The reason for this may be caused by the following: (1) Because gene mutations such as EGFR/ALK/ROS1/RET are very common in female NSCLC in China, many female patients receive targeted therapy instead of immunotherapy; (2) The patients we included were predominantly squamous cancer (62.1%), there is a higher proportion of male than female in squamous lung carcinoma; (3) It may be related to the national situation in China, where the use of pembrolizumab is self-funded, and in the overall gender tendency will be more in favor of male. Secondly, not all patients underwent regular TFTs, sex hormone, cortisol, ACTH tests and blood glucose monitoring before each treatment with pembrolizumab. Thirdly, some patients received pembrolizumab for a short period, resulting in limited availability of post-treatment data. This restricts our ability to capture the full extent of E-irAE in these cases. Fourthly, there were instances where the assessment of antibodies, a possible predictor of irTD, was missing. This limitation may be attributed to insufficient recognition and monitoring of these predictors during the study period. Therefore, to address these limitations and obtain a more comprehensive understanding of E-irAE, further studies with larger sample sizes and standardized monitoring protocols are warranted.

Conclusion

Our retrospective study provided insights into the clinical / biochemical features of E-irAE in Chinese NSCLC patients. Given the increasing use of ICIs, irAEs also become an important part of oncology practice. In our cohort, we observed that TGAb positivity and a low MLR level at baseline were associated with the development of irTD. TSH level at baseline may also predict the onset of irTD, except for Ohe. Additionally, the presence of irTD and male were identified as independent protective factors associated with a longer PFS. Nevertheless, this study still had some limitations. Prospective large-scale studies would be necessary to further evaluate these findings and address the remaining uncertainties surrounding E-irAE in patients with NSCLC.

Abbreviations

NSCLC	Non-small cell lung cancer
irAEs	Immune-related adverse events
E-irAE	Immune-related endocrine toxicities
irTD	Immune-related thyroid dysfunction
ICI	Immune checkpoint inhibitors
PFS	Progression free survival
MLR	Monocyte-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio
NLR	Neutrophil-to-lymphocyte ratio
TSH	Thyroid-stimulating hormone
FT3	Free Triiodothyronine
FT4	Free thyroxine
TPOAb	Thyroid peroxidase antibody
TGAb	Anti-thyroglobulin antibody
OR	Odds ratio
CI	Confidence interval
HR	Hazard ratio
PD-1/PD-L1	Programmed death-1/Programmed death ligand-1
OS	Overall survival
BMI	Body mass index
ECOG-PS	Eastern Cooperative Oncology Group-performance status
TFTs	Thyroid function tests
IQR	Interquartile range
T1DM	Type 1 diabetes mellitus
GAD	Glutamic acid decarboxylase
IA2	Insulin Antibody
ICA	Islet cell antibody
ACTH	Adrenocorticotrophic hormone
FSH	Follicle-stimulating hormone
LH	Luteinizing hormon
PRL	Prolactine
CRP	C-reactive protein
LDH	Lactate dehydrogenase
IH	Hypophysitis
DM	Immune-related diabetes mellitus
PAI	Immune-related primary adrenal insufficiency
Oho	Overt hypothyroidism
Scho	Subclinical hypothyroidism

Ohe	Overt hyperthyroidism
Sche	Subclinical hyperthyroidism

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Author contributions
H.Z., J.Z., C.R., C.Y., X.W., X.L. and Y.L. provided the raw data. H.Z. and J.Z. conducted the statistical analysis. The first draft of the manuscript was written by H.Z., J.Z. and H.Z. carefully edited and guided writing of the manuscript. J.Z. and J.Z. are co-corresponding authors. All authors contributed to the article and approved the final manuscript.

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Data availability
The datasets used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval
All experiments were performed in accordance with relevant guidelines and regulations (such as the Declaration of Helsinki). This study was reviewed and approved by the Ethical Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University on October 24th (Number: 2019 – 1433) and by the Ethical Committee of the Fourth Affiliated Hospital, College of Medicine, Zhejiang University on November 13th (Number: 20231108). Given the retrospective nature of this study, informed consent exemption was obtained for this study from Ethics Committee of the First Affiliated Hospital of Zhejiang University, the Fourth Affiliated Hospital of Zhejiang University, Guangfu Hospital, Affiliated Hospital of Jiaxing University and the First Affiliated Hospital Wenzhou Medical College.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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