Original Article

Hypothyroidism induced by immune checkpoint inhibitors combined with antiangiogenic agents is associated with higher body mass index

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Background: Recent studies have reported that the combination of immune checkpoint inhibitors (ICIs) and antiangiogenic agents could be a promising therapeutic strategy for advanced non-small cell lung cancer (NSCLC). However, both ICIs and antiangiogenic agents are associated with endocrine dysfunctions, mainly hypothyroidism. The risk of hypothyroidism is potentially increased with the combination of ICIs and antiangiogenic agents. This study aimed to investigate the incidence and risk factors of hypothyroidism in patients receiving combination therapy.

Methods: We performed a retrospective cohort study of advanced NSCLC patients treated with ICIs and antiangiogenic agents at Tianjin Medical University Cancer Institute & Hospital from July 1, 2019, to December 31, 2021. Patients with normal thyroid function at baseline were enrolled, and information on the patients' characteristics before receiving combination therapy, including body mass index (BMI) and laboratory data, was obtained.

Results: Among the 137 enrolled patients, 39 (28.5%) developed new-onset hypothyroidism, and 20 (14.6%) developed overt hypothyroidism. The incidence of hypothyroidism was significantly higher in obese patients than in patients with a low to normal BMI (P<0.001). Obese patients also had a higher incidence of overt hypothyroidism (P=0.016). Univariate logistic regression showed that BMI as a continuous variable was a significant risk factor for hypothyroidism [odds ratio (OR) 1.24, 95% confidence interval (CI): 1.10–1.42, P<0.001] and overt hypothyroidism (OR 1.17, 95% CI: 1.01–1.38, P=0.039). Multivariate logistic regression revealed that only BMI (OR 1.36, 95% CI: 1.16–1.61, P<0.001) and age (OR 1.08, 95% CI: 1.02–1.14, P=0.006) were significant risk factors for treatment-related hypothyroidism.

Conclusions: The risk of hypothyroidism in patients receiving a combination of ICIs and antiangiogenic therapy is manageable, and a higher BMI is associated with a significantly increased risk of hypothyroidism. Therefore, clinicians should be aware of the development of hypothyroidism in obese advanced NSCLC patients during the administration of ICIs combined with antiangiogenic agents.

Keywords: Hypothyroidism; immune checkpoint inhibitor (ICI); antiangiogenic agent; body mass index (BMI); logistic regression

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Introduction

Immune checkpoint inhibitors (ICIs) are often used to treat non-small cell lung cancer (NSCLC); however, many patients do not benefit from these therapies. Studies have shown that the combination of ICIs and antiangiogenic medicines is effective and safe in the treatment of advanced NSCLC (1,2). The IMPOWER 150 study demonstrated that atezolizumab combined with bevacizumab prolonged the progression-free survival and overall survival of patients with advanced NSCLC (3,4). The overall effectiveness and safety of pembrolizumab coupled with ramucirumab for the treatment of patients with advanced NSCLC were good, as reported in the JVDF trial (5). In the phase II Passion study, camrelizumab combined with apatinib demonstrated good efficacy and safety in the treatment of advanced NSCLC (6). However, both ICIs and antiangiogenic agents cause a number of adverse effects, and the toxicity spectrum can be more complex when used together than when used alone.

Thyroid dysfunction, such as hypothyroidism, hyperthyroidism, and thyroiditis, has been documented in up to 50% of patients treated with ICI-based combination therapies in several trials (6-9). Notably, a previous study (10) reported that combination immunotherapy was associated with a high estimated incidence of high thyroid dysfunction frequencies, ranging from 8.0% to 16.4%, which is significantly higher than that of monotherapy with programmed cell death-1 (PD-1), programmed cell death ligand 1 (PD-L1) inhibitors, or drugs targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). In addition, studies have also demonstrated that patients who receive antiangiogenic monoclonal antibodies and small molecule anti-vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs) have a significantly increased risk of hypothyroidism (11-13).

The endocrine toxicities caused by immune therapy combined with antiangiogenic agents have rarely been studied. A previous systematic review (14) showed that the total incidence of severe adverse events (AEs) associated with ICIs plus antiangiogenic monoclonal antibodies (mAbs) is lower than that of ICIs plus TKIs. The most commonly reported AEs of immune therapy combined with antiangiogenic agents included thrombocytopenia and fatigue, while nausea, vomiting, and immune pneumonia were relatively rare. Another retrospective cohort study including three clinical trials in patients with stage III/IV melanoma treated with anti-PD-1 and antiangiogenic therapy showed that the treatment-related AEs (trAEs) mainly affected the liver, endocrine, skin, and gastrointestinal tract, followed by myelosuppression, renal insufficiency, and dyslipidemia (15). Overall, the trAE spectra are similar to those found in ICIs or antiangiogenic treatment monotherapy and are not severe.

Recent studies investigated the potential risk factors of thyroid immune-related AEs (irAEs). Specifically, the presence of baseline thyroid autoantibodies and the number of ICI treatment cycles were associated with an increased risk (16-18). Emerging evidence has suggested that the increased irAEs in cancer patients receiving ICIs are linked to the obese and overweight body mass index (BMI) categories (19). Obesity is a low-grade inflammatory metabolic condition associated with many coexisting diseases, including diabetes, cardiovascular disease, and cancer (20-25).

It is speculated that the combined use of ICIs and antiangiogenic agents may increase the risk and complexity of hypothyroidism. Based on this hypothesis, we intend to evaluate the incidence of hypothyroidism in NSCLC patients receiving ICIs combined with antiangiogenic agents, evaluate the risk factors of hypothyroidism caused by ICIs combined with antiangiogenic therapy, and explore the relationship between BMI and treatment-related hypothyroidism. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-306/rc).

Highlight box

Key findings

- High body mass index (BMI) is associated with hypothyroidism induced by immune checkpoint inhibitors (ICIs) plus antiangiogenic agents.

What is known and what is new?

- Hypothyroidism is often observed in patients receiving immune checkpoint blockade, and antiangiogenic agents are also known to be associated with hypothyroidism. However, the incidence rate and risk factors of hypothyroidism caused by ICIs combined with antiangiogenic therapy are still not well understood.
- A 28.5% incidence rate of any grade hypothyroidism was reported in this cohort. The logistic analysis demonstrated that a higher BMI was significantly associated with an increased risk of hypothyroidism induced by ICIs plus antiangiogenic agents.

What is the implication, and what should change now?

- Our findings demonstrate that although the risk of hypothyroidism in patients receiving a combination of ICIs and antiangiogenic agents is manageable, clinicians should perform regular thyroid function monitoring in high-risk groups during the combination therapy.

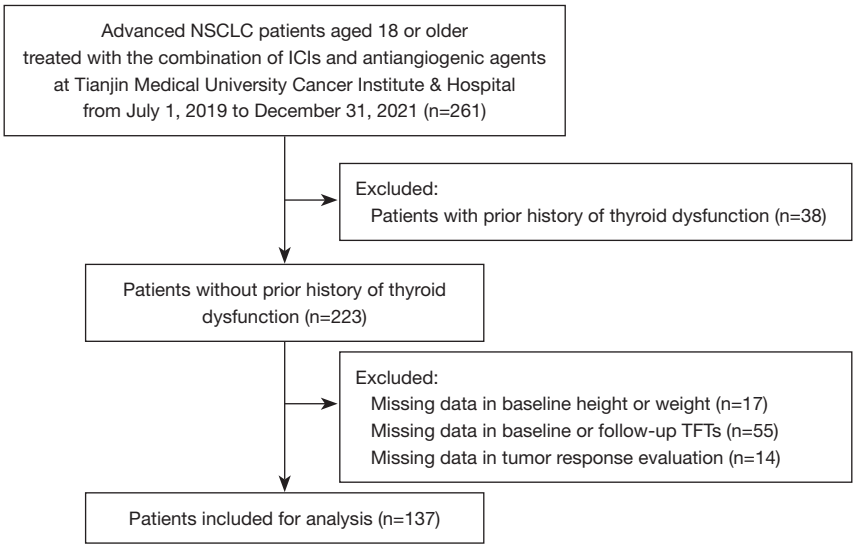

Figure 1 Flow diagram of the study. NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; BMI, body mass index; TFTs, thyroid function tests.

Methods

Study design and participants

We conducted a retrospective study using data from the Tianjin Medical University Cancer Institute & Hospital. This study included patients with advanced NSCLC aged 18 or older who received PD-1 inhibitors (nivolumab, pembrolizumab, tislelizumab, camrelizumab, sintilimab) or PD-L1 inhibitors (durvalumab, atezolizumab) combined with antiangiogenic therapy (bevacizumab, anlotinib, apatinib) in our hospital from July 1, 2019, to December 31, 2021. The patients' complete medical data were recorded in electronic medical records, including medical diagnoses, laboratory tests, prescription drugs, follow-up information, etc. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional Ethics Committee of Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin, China (approval number: bc2022098). Due to the anonymity of patient records, the individual consent for this retrospective analysis was waived.

Baseline assessments were defined as those taken within 2 weeks before the administration of combined therapy. Patient characteristics and clinical data included age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), smoking status, histology, comorbidities, combination therapy with or without chemotherapy, PD-L1 expression, ICI drug target, treatment line, height, and weight. The baseline laboratory test variables, including white blood cell count, neutrophil count, lymphocyte count, platelet count, monocyte count, eosinophil count, hemoglobin, and albumin, were analyzed as continuous variables. In addition, thyroid function tests (TFTs) within 1 month before the treatment start date, including records of thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3), were collected. Specifically, a TFT was required before each treatment cycle, and at least five TFTs were recorded during the treatment. The related symptoms of abnormal thyroid function were also collected. Patients with a history of thyroid dysfunction prior to treatment, including a previously diagnosed thyroid dysfunction listed in the medical history, who had previously received antithyroid drugs or levothyroxine treatment, or if the TFT was abnormal at baseline, were excluded. We also excluded cases with missing values, including 17 cases without baseline height or weight data, 55 patients with missing TFTs during the follow-up, and 14 patients for whom we were unable to evaluate the response. Tumor responses were evaluated using the Response Evaluation Criteria for Solid Tumors version 1.1. The median follow-up time was 10.9 months. The study flow diagram is shown in *Figure 1*.

BMI assessment

BMI was calculated using patients' height and weight,

which was measured within 2 weeks before combination treatment initiation, and was analyzed as both a continuous and a categorized variable. The patients were categorized into three categories based on their baseline BMI, according to the World Health Organization (WHO) Regional Committee for the Western Pacific standard (26): low-normal BMI <23 kg/m^2; overweight 23–24.9 kg/m^2; obese >25 kg/m^2.

Assessment of outcomes

Hypothyroidism outcomes were defined as follows: (I) any hypothyroidism (overt and subclinical) was defined as a TSH level greater than the laboratory-specific reference range, regardless of the fT4 and fT3 values during follow-up; (II) overt hypothyroidism was defined as decreased fT4 levels and/or decreased fT3 levels, or elevated TSH levels of 10 mIU/L or higher; (III) subclinical hypothyroidism was defined as TSH greater than the laboratory-specific reference range but <10 mIU/L, and without a corresponding fT4 or fT3 exception. The multiple definitions of the study outcomes were used to evaluate the robustness of the results.

Statistical analysis

Continuous variables were described as the mean ± standard deviation. Comparisons between two outcome groups were performed using either the Student's *t*-test, Wilcoxon rank sum test, Chi-square test, or Fisher's exact test, as appropriate. A logistic regression model was employed in the univariate and multivariate analysis to identify risk factors for any grade hypothyroidism or overt hypothyroidism, and multivariate logistic analysis was conducted to reduce the effects of potential confounders. Backward stepwise elimination based on the Wald test was used to reduce the number of predictors in the multivariable logistic regression models, as the sample size was comparatively small and the prevalence of outcome was relatively low, and a liberal P value of 0.10 was used. Two variables were introduced in a multivariable logistic regression model predicting hypothyroidism, and one predictor was introduced in the model predicting overt hypothyroidism. Therefore, the sample size of this study was considered suitable to obtain accurate results. All P values presented were two-sided. P<0.05 was deemed statistically significant. R software was used for all statistical analyses (version 4.2.1, R Foundation, Vienna, Austria).

Results

Study population characteristics

A total of 137 patients were enrolled in this study. The clinical characteristics of all included patients are shown in *Table 1*. The average age of the patients was 61.12±9.41 years old, and the average BMI of the patients was 23.90±3.31 kg/m^2. This cohort was dominated by male patients (82.5%) and patients with ECOG-PS of 0 or 1 (86.1%). The majority of patients (71.5%) were current or former smokers. Squamous cell carcinoma histology accounted for 35.8% of the subjects. The combination of ICIs, antiangiogenesis agents, and chemotherapy was administered to 42.3% of patients in our cohort. Most of the patients (80.3%) received the combination regimen as a first- or second-line therapy. Among this cohort, the objective response rate was 35.8%.

Comparisons of characteristics in patients with and without hypothyroidism

As shown in *Table 2*, 39 (28.5%) of the 137 patients developed hypothyroidism. Among them, 20 cases (14.6%) were overt hypothyroidism and 19 cases (13.9%) were subclinical hypothyroidism. Of the 39 patients with hypothyroidism, 17 received levothyroxine replacement therapy, and only one of them required steroids and discontinuation of therapy.

The average BMI of patients with hypothyroidism was significantly higher than that of patients with normal thyroid function (25.46±3.25 *vs.* 23.28±3.14, P<0.001), and their age was also significantly older than that of patients with normal thyroid function (64.59±7.19 *vs.* 59.74±9.85, P=0.006). The mean baseline BMI was also significantly higher in patients who developed overt hypothyroidism than that of the other patients (25.33±2.77 *vs.* 23.65±3.34, P=0.035), while the distribution of their baseline characteristics other than BMI was similar to that of the other patients. Moreover, there was no significant difference in the laboratory examination results between patients with and without hypothyroidism or in the proportion of tumor response between the outcome groups.

Logistic regression analyses of the risk of hypothyroidism

In the univariate logistic regression analyses, we analyzed BMI as a continuous variable and found that the risk of

Table 1 Baseline characteristics of the included patients

Variables	Total, n=137
Age (years)	61.12 (9.41)
Gender	
Female	24 [17.5]
Male	113 [82.5]
ECOG-PS	
0	51 [37.2]
1	67 [48.9]
2	19 [13.9]
Smoking history	
Never	39 [28.5]
Current or former	98 [71.5]
Histology	
Non-squamous	88 [64.2]
Squamous	49 [35.8]
Diabetes, n (%)	
Without	118 [86.1]
With	19 [13.9]
Combined chemotherapy	
Without	79 [57.7]
With	58 [42.3]
PD-L1 expression	
<1%	27 [19.7]
≥1%	35 [25.6]
Unknown	75 [54.7]
ICI drug target	
PD-L1	10 [7.3]
PD-1	127 [92.7]
Line of ICI therapy	
1	44 [32.1]
2	66 [48.2]
≥3	27 [19.7]
Best tumor response	
PR	49 [35.8]
SD	69 [50.3]
PD	19 [13.9]
BMI (kg/m^2)	23.90 (3.31)
BMI	
Low-normal	56 [40.9]
Overweight	31 [22.6]
Obese	50 [36.5]
WBC (10^9/L)	7.00 (2.65)
NEU (10^9/L)	5.82 (8.06)
LYM (10^9/L)	1.86 (3.22)
PLT (10^9/L)	254.39 (97.45)
MONO (10^9/L)	0.61 (0.28)
AEC (10^9/L)	0.20 (0.31)
Hb (g/L)	129.45 (20.65)
ALB (g/L)	94.55 (28.60)

Values are expressed as the mean (standard deviation) or n [%]. ECOG-PS, the Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death protein ligand-1; PD-1, programmed cell death protein-1; ICI, immune checkpoint inhibitor; PR, partial response; SD, stable disease; PD, progressive disease; BMI, body mass index; WBC, white blood cell count; NEU, neutrophil count; LYM, lymphocyte count; PLT, platelet count; MONO, monocytes count; AEC, absolute eosinophil count; Hb, hemoglobin; ALB, albumin.

hypothyroidism continued to increase with the increase in BMI [odds ratio (OR) 1.24, 95% confidence interval (CI): 1.10–1.42; P<0.001, *Table 3* and *Figure 2A*]. BMI was also a significant risk factor for overt hypothyroidism (OR 1.17, 95% CI: 1.01–1.38, P=0.039, *Table 4* and *Figure 2B*). The multivariate logistic regression analysis showed that baseline BMI (OR 1.36, 95% CI: 1.16–1.61, P<0.001) and age (OR 1.08, 95% CI: 1.02–1.14, P=0.006, *Table 3*) were independent predictors of hypothyroidism. Furthermore, the multivariate analysis also showed that only BMI was an independent risk factor for overt hypothyroidism (OR =1.23, 95% CI: 1.03–1.52, P=0.029, *Table 4*).

Discussion

This study assessed the incidence of hypothyroidism in patients with advanced NSCLC who received PD-1 or PD-L1 inhibitors combined with antiangiogenic therapy, examined the hypothyroidism-related risk factors, and

Table 2 Comparison of the characteristics between the outcome groups

Variables	Any hypothyroidism			Subclinical hypothyroidism			Overt hypothyroidism		
	+ (n=39)	– (n=98)	P value	+ (n=19)	– (n=118)	P value	+ (n=20)	– (n=117)	P value
Age (years)	64.59 (7.19)	59.74 (9.85)	0.006*	66.63 (6.65)	60.24 (9.51)	0.006*	62.65 (7.31)	60.86 (9.72)	0.435
Gender			0.869			1.000			0.998
Female	6 [15.4]	18 [18.4]		3 [15.8]	21 [17.8]		3 [15.0]	21 [17.9]	
Male	33 [84.6]	80 [81.6]		16 [84.2]	97 [82.2]		17 [85.0]	96 [82.1]	
ECOG-PS			0.645			0.694			0.286
0	13 [33.3]	38 [38.8]		6 [31.6]	45 [38.1]		7 [35.0]	44 [37.6]	
1	19 [48.7]	48 [49.0]		11 [57.9]	56 [47.5]		8 [40.0]	59 [50.4]	
2	7 [18.0]	12 [12.2]		2 [10.5]	17 [14.4]		5 [25.0]	14 [12.0]	
Smoking history			0.131			0.619			0.240
Never	7 [17.9]	32 [32.7]		4 [21.1]	35 [29.7]		3 [15.0]	36 [30.8]	
Current or former	32 [82.1]	66 [67.3]		15 [78.9]	83 [70.3]		17 [85.0]	81 [69.2]	
Histology			0.859			0.879			1.000
Non-squamous	26 [66.7]	62 [63.3]		13 [68.4]	75 [63.6]		13 [65.0]	75 [64.1]	
Squamous	13 [33.3]	36 [36.7]		6 [31.6]	43 [36.4]		7 [35.0]	42 [35.9]	
Diabetes			1.000			0.536			0.373
Without	34 [87.2]	84 [85.7]		15 [78.9]	103 [87.3]		19 [95.0]	99 [84.6]	
With	5 [12.8]	14 [14.3]		4 [21.1]	15 [12.7]		1 [5.0]	18 [15.4]	
Combined chemotherapy			0.446			1.000			0.319
Without	20 [51.3]	59 [60.2]		11 [57.9]	68 [57.6]		9 [45.0]	70 [59.8]	
With	19 [48.7]	39 [39.8]		8 [42.1]	50 [42.4]		11 [55.0]	47 [40.2]	
PD-L1 expression			0.916			0.711			0.825
<1%	8 [20.5]	19 [19.4]		5 [26.3]	22 [18.6]		3 [15.0]	24 [20.5]	
≥1%	9 [23.1]	26 [26.5]		4 [21.1]	31 [26.3]		5 [25.0]	30 [25.6]	
Unknown	22 [56.4]	53 [54.1]		10 [52.6]	65 [55.1]		12 [60.0]	63 [53.9]	
ICI drug target			0.229			0.914			0.333
PD-L1	5 [12.8]	5 [5.1]		2 [10.5]	8 [6.8]		3 [15.0]	7 [6.0]	
PD-1	34 [87.2]	93 [94.9]		17 [89.5]	110 [93.2]		17 [85.0]	110 [94.0]	
Line of ICI therapy			0.215			0.502			0.452
1	14 [35.9]	30 [30.6]		6 [31.6]	38 [32.2]		8 [40.0]	36 [30.8]	
2	21 [53.8]	45 [45.9]		11 [57.9]	55 [46.6]		10 [50.0]	56 [47.8]	
≥3	4 [10.3]	23 [23.5]		2 [10.5]	25 [21.2]		2 [10.0]	25 [21.4]	

Table 2 *(continued)*

Table 2 *(continued)*

Variables	Any hypothyroidism			Subclinical hypothyroidism			Overt hypothyroidism		
	+ (n=39)	– (n=98)	P value	+ (n=19)	– (n=118)	P value	+ (n=20)	– (n=117)	P value
Best tumor response, n (%)			0.876			0.902			0.844
PR	13 [33.3]	36 [36.7]		7 [36.9]	42 [35.6]		6 [30.0]	43 [36.7]	
SD	21 [53.9]	48 [49.0]		10 [52.6]	59 [50.0]		11 [55.0]	58 [49.6]	
PD	5 [12.8]	14 [14.3]		2 [10.5]	17 [14.4]		3 [15.0]	16 [13.7]	
BMI (kg/m^2)	25.46 (3.25)	23.28 (3.14)	<0.001*	25.60 (3.77)	23.63 (3.16)	0.015*	25.33 (2.77)	23.65 (3.34)	0.035*
BMI			<0.001*			0.032*			0.016*
Low-normal	8 [20.5]	48 [49.0]		4 [21.0]	52 [44.1]		4 [20.0]	52 [44.4]	
Overweight	6 [15.4]	25 [25.5]		3 [15.8]	28 [23.7]		3 [15.0]	28 [24.0]	
Obese	25 [64.1]	25 [25.5]		12 [63.2]	38 [32.2]		13 [65.0]	37 [31.6]	
WBC (10^9/L)	7.14 (2.18)	6.95 (2.82)	0.716	7.20 (2.55)	6.97 (2.67)	0.734	7.08 (1.82)	6.99 (2.77)	0.895
NEU (10^9/L)	4.86 (1.77)	6.21 (9.45)	0.379	5.16 (2.01)	5.93 (8.65)	0.702	4.57 (1.49)	6.04 (8.69)	0.454
LYM (10^9/L)	1.50 (0.68)	2.00 (3.78)	0.413	1.33 (0.65)	1.95 (3.45)	0.439	1.67 (0.69)	1.89 (3.47)	0.772
PLT (10^9/L)	254.82 (87.27)	254.22 (101.64)	0.974	260.05 (97.47)	253.48 (97.83)	0.786	249.85 (78.60)	255.17 (100.58)	0.823
MONO (10^9/L)	0.59 (0.20)	0.62 (0.30)	0.661	0.59 (0.23)	0.61 (0.28)	0.735	0.60 (0.18)	0.61 (0.29)	0.820
AEC (10^9/L)	0.15 (0.12)	0.22 (0.36)	0.269	0.14 (0.11)	0.21 (0.33)	0.337	0.17 (0.13)	0.20 (0.33)	0.639
Hb (g/L)	128.64 (18.21)	129.78 (21.62)	0.773	127.16 (22.84)	129.82 (20.36)	0.604	130.05 (12.83)	129.35 (21.74)	0.889
ALB (g/L)	41.53 (5.05)	40.81 (4.83)	0.440	42.98 (6.19)	40.70 (4.60)	0.059	40.16 (3.25)	41.17 (5.11)	0.395

Values are expressed as the mean (standard deviation) or n [%]. *, significant P values <0.05. ECOG-PS, the Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death protein ligand-1; PD-1, programmed cell death protein-1; ICI, immune checkpoint inhibitor; PR, partial response; SD, stable disease; PD, progressive disease; BMI, body mass index; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; PLT, platelet; MONO, monocytes; AEC, absolute eosinophil count; Hb, hemoglobin; ALB, albumin.

analyzed the effect of baseline BMI on treatment-related hypothyroidism. Overall, 39 cases (28.5%) developed hypothyroidism and 20 cases (14.6%) developed overt hypothyroidism. The observed incidence rate was consistent with those reported in previous studies (18,19,27-29). Our data confirmed no significant increase in the incidence of any grade and overt hypothyroidism in patients who received combination treatment with ICIs and antiangiogenetic agents. Patients with a higher BMI had an increased risk of developing any grade or overt hypothyroidism, which was consistent with the findings of an ICI monotherapy cohort study (19). Our findings suggest that the risk of hypothyroidism with combination therapy might be manageable, mitigating the concern regarding the synergy between the two endocrine toxicity mechanisms.

It is known that hypothyroidism is a common AE during antiangiogenic therapy. Blockade of the VEGF pathway may potentially cause thyroid dysfunction possibly via the following mechanism: Systemic administration of anti-VEGF medications decreases thyroid vascular density and fenestrations, which results in hypothyroidism since VEGF is essential for vascular homeostasis as well as the preservation of vascular integrity and thyroid gland architecture (30). Although hypothyroidism is modest among all irAEs, it is associated with significant morbidity (31,32). The underlying mechanism of ICI-related thyroid dysfunction remains unknown; however, based on the fact that the thyroid gland is more susceptible to autoimmune attacks than any other organ, coupled with the important role of endocrine-specific autoantibodies in the pathogenesis of endocrine-related AEs, it is thought to be caused by impaired the immune tolerance of autoantigens and thyroid

Table 3 Predictors associated with any hypothyroidism

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (continuous)	1.07 (1.02–1.12)	0.008*	1.08 (1.02–1.14)	0.006*
Gender (female/male)	1.24 (0.47–3.66)	0.679	–	–
ECOG-PS (0–1/2)	1.57 (0.54–4.26)	0.386	–	–
Smoking (never/current or former)	2.22 (0.92–5.95)	0.090	–	–
Histology (non-squamous/squamous)	0.86 (0.39–1.86)	0.708	–	–
Diabetes (without/with)	0.88 (0.27–2.51)	0.823	–	–
Combined chemotherapy (without/with)	1.44 (0.68–3.04)	0.341	–	–
ICI drug target (PD-L1/PD-1)	0.37 (0.10–1.39)	0.129	–	–
Line of ICI therapy (continuous)	0.69 (0.40–1.17)	0.171	–	–
Best tumor response (PR + SD/PD)	1.19 (0.39–3.28)	0.746	–	–
BMI (continuous)	1.24 (1.10–1.42)	<0.001*	1.36 (1.16–1.61)	<0.001*
WBC (continuous)	1.03 (0.89–1.18)	0.714	–	–
NEU (continuous)	0.97 (0.86–1.02)	0.418	–	–
LYM (continuous)	0.90 (0.57–1.06)	0.489	–	–
PLT (continuous)	1.00 (1.00–1.00)	0.974	–	–
MONO (continuous)	0.73 (0.17–2.82)	0.658	–	–
AEC (continuous)	0.38 (0.04–1.60)	0.286	–	–
Hb (continuous)	1.00 (0.98–1.02)	0.771	–	–
ALB (continuous)	1.03 (0.96–1.12)	0.437	–	–

*, significant P values <0.05. ECOG-PS, the Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death protein ligand-1; PD-1, programmed cell death protein-1; ICI, immune checkpoint inhibitor; PR, partial response; SD, stable disease; PD, progressive disease; BMI, body mass index; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; PLT, platelet; MONO, monocytes; AEC, absolute eosinophil count; Hb, hemoglobin; ALB, albumin; OR, odds ratio; CI, confidence interval.

cell destruction, similar to autoimmune thyroid disorders (33,34). The use of ICIs combined with antiangiogenic drugs may increase the complexity of toxicity management because some of the AEs of ICIs are similar to those of antiangiogenic therapy. Accurate identification of the cause of each type of hypothyroidism is important but may not always be possible. The identification of risk factors is also crucial to further understanding the mechanism affecting thyroid function and minimizing the treatment-related AEs.

Numerous studies have confirmed the association between obesity and autoimmune thyroid disease, including immunotherapy-related thyroid dysfunction (19,35-38). BMI is an alternative indicator of body fat; one study showed that BMI plays a role in the complex interaction between inflammation and immune dysfunction in patients treated with PD-1 or PD-L1 inhibitors (19). Mechanically, previous studies have shown that the increased prevalence of thyroid dysfunction and thyroid autoantibodies in obese people may be related to increased leptin levels (37) and chronic inflammation caused by obesity (39).

Age has also been thought to be associated with hypothyroidism, possibly because TSH levels increase with age. The underlying mechanism of this relationship may be that the increase of TSH levels in the elderly is due to its decreased biological activity or the reduced thyroid responsiveness to TSH. This is evidenced by the lack of a concurrent decline in T4 levels, suggesting that this is a physiological adaptation process. Therefore, the occurrence of subclinical hypothyroidism in the elderly may have no clinical significance (40). Our results showed that age was

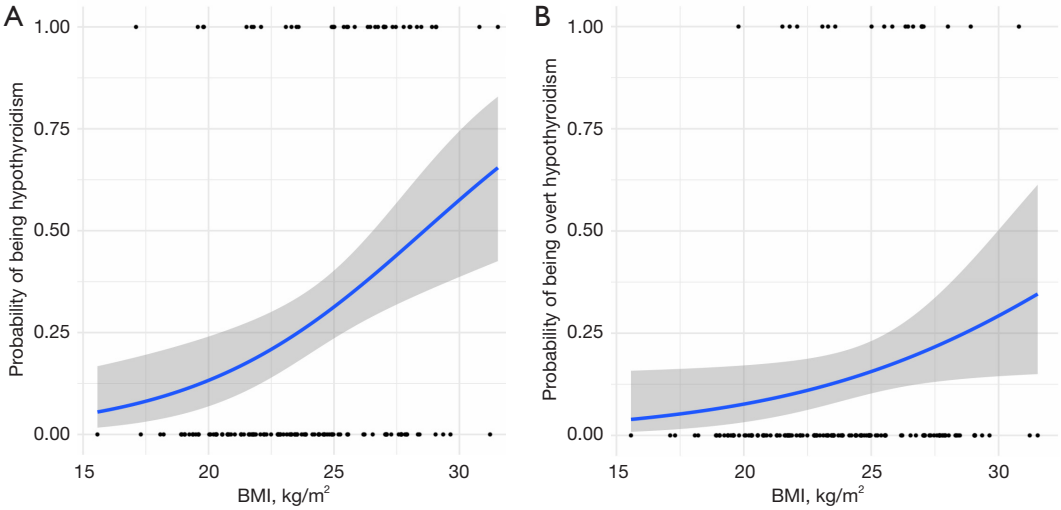

Figure 2 Association between BMI and the probability of outcomes. (A) The probability (95% CI) of developing hypothyroidism by baseline BMI; (B) the probability (95% CI) of developing overt hypothyroidism by baseline BMI. BMI, body mass index; CI, confidence interval.

Table 4 Predictors associated with overt hypothyroidism

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (continuous)	1.02 (0.97–1.08)	0.432	–	–
Gender (female/male)	1.24 (0.37–5.65)	0.749	–	–
ECOG-PS (0–1/2)	2.45 (0.71–7.50)	0.128	–	–
Smoking (never/current or former)	2.52 (0.78–11.27)	0.160	–	–
Histology (non-squamous/squamous)	0.96 (0.34–2.54)	0.938	–	–
Diabetes (without/with)	0.29 (0.02–1.54)	0.241	–	–
Combined chemotherapy (without/with)	1.82 (0.70–4.84)	0.219	–	–
ICI drug target (PD-L1/PD-1)	0.36 (0.09–1.79)	0.167	–	–
Line of ICI therapy (continuous)	0.65 (0.32–1.29)	0.233	–	–
Best tumor response (PR + SD/PD)	1.11 (0.24–3.81)	0.874	–	–
BMI (continuous)	1.17 (1.01–1.38)	0.039*	1.23 (1.03–1.52)	0.029*
WBC (continuous)	1.01 (0.83–1.19)	0.894	–	–
NEU (continuous)	0.95 (0.75–1.03)	0.503	–	–
LYM (continuous)	0.97 (0.65–1.11)	0.775	–	–
PLT (continuous)	1.00 (0.99–1.00)	0.821	–	–
MONO (continuous)	0.81 (0.12–4.36)	0.818	–	–
AEC (continuous)	0.63 (0.04–2.86)	0.640	–	–
Hb (continuous)	1.00 (0.98–1.03)	0.888	–	–
ALB (continuous)	0.96 (0.87–1.06)	0.393	–	–

*, significant P values <0.05. ECOG-PS, the Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death protein ligand-1; PD-1, programmed cell death protein-1; ICI, immune checkpoint inhibitor; PR, partial response; SD, stable disease; PD, progressive disease; BMI, body mass index; WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; PLT, platelet; MONO, monocytes; AEC, absolute eosinophil count; Hb, hemoglobin; ALB, albumin; OR, odds ratio; CI, confidence interval.

only associated with subclinical hypothyroidism but had no predictive significance for overt hypothyroidism, which confirms the above perspective, indicating that steroids or interruption of the combination therapy may not be needed in elderly patients with only a slight increase in TSH.

Several limitations of our study should be noted and considered. Firstly, given that this study was a single-center retrospective study with a relatively small sample size, further research is needed to verify whether the results can be extrapolated to other populations. Secondly, we were unable to obtain the baseline thyroid peroxidase antibodies status of patients, which may limit our investigation into the predictive influence of baseline antibody status on the incidence of hypothyroidism. Thirdly, we did not report on the overall survival of patients in this cohort, and thus, were unable to analyze the relationship between BMI and survival or hypothyroidism and survival. Interestingly, multiple research groups have found an improvement in progression-free and overall survival in obese patients treated with PD-(L)1 checkpoint inhibitors (20,41). Large real-world observational study has also confirmed that baseline obesity is significantly associated with improved objective response rate, progression-free survival, and overall survival in metastatic non-small cell lung cancer patients with a PD-L1 expression of ≥50%, receiving first-line single-agent pembrolizumab, and that there is a significant improvement in ORR, PFS, and OS in patients with slight weight gain during immunotherapy (42). Finally, since the interval between TFTs was not uniform in our study, we were unable to accurately evaluate the time of the initial incidence of hypofunction. Future studies should use multi-center, prospective designs with standardized follow-up intervals to obtain reliable and comprehensive data on hypothyroidism risk in patients receiving immune checkpoint blockade and antiangiogenic therapy, and it would be valuable to investigate the predictive value and mechanisms of obesity on the efficacy and survival of immune checkpoint inhibitors and anti-angiogenic therapy, and assess clinical implications to improve lung cancer treatment outcomes.

Conclusions

Our findings suggest that the risk of hypothyroidism in patients receiving combination treatment with ICIs and antiangiogenic agents is manageable, and a higher BMI is associated with a significantly increased risk of treatment-related hypothyroidism. Clinicians should be aware of these risks and perform regular thyroid function monitoring in high-risk groups during the administration of combination therapy with immune checkpoint blockade and antiangiogenic agents.

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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-23-306/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-306/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-306/coif). The authors have no conflicts of interest to declare.

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 approved by the institutional Ethics Committee of Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin, China (approval number: bc2022098). Due to the anonymity of patient records, the individual consent for this retrospective analysis was waived.

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