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RESEARCH

Transarterial chemoembolization combined with tyrosine kinase inhibitors and/or immune checkpoint inhibitors induced hypothyroidism is associated with improved overall survival in hepatocellular carcinoma

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Abstract
Hepatocellular carcinoma (HCC) treatments, including transarterial chemoembolization (TACE) and systemic therapies (tyrosine kinase inhibitors [TKIs]/immune checkpoint inhibitors [ICIs]) are linked to hypothyroidism. This study aims to elucidate the clinical significance of treatment-induced hypothyroidism within a real-world cohort. We enrolled 130 HCC patients with baseline thyroid function measurements, and stratified into two cohorts: TACE monotherapy (n = 50) or TACE combined with TKIs/ICIs (n = 80). Primary subclinical or obvious hypothyroidism patients have a serum thyroid-stimulating hormone (TSH) value exceeding the upper limit of the normal range (> 4.94 uIU/L) while thyroid free tetraiodothyronine levels are normal or low. Overall survival (OS) was evaluated via Kaplan–Meier and Cox proportional models. Mortality rate in the whole study population was 25% (13/52) in patients with hypothyroidism vs. 48.7% (38/78) in patients without hypothyroidism (P = 0.007). When using TACE combining TKIs and ICIs, the mortality rate of patients with hypothyroidism were less than that of patients without hypothyroidism (16% [4/25] vs. 50% [8/16], respectively; P = 0.02). For entire cohort, the median OS cutoff in patients with hypothyroidism reached 37.5 months, and median OS was 23.33 months in patients without hypothyroidism (P = 0.015). For patients treated with TACE combined with TKIs + ICIs, the median OS cutoff in patients with hypothyroidism was not reached. But it was longer than those without hypothyroidism where median OS was 22.54 months (P = 0.005). In univariate and multivariate analysis, cancer-specific mortality correlated with some factors including sex, drinking, and hypothyroidism in the whole population as well as subgroups received TACE only or combination. In all patients, after adjustment for confounding factors, drinking showed an increased risk of HCC mortality (HR: 1.94, 95% CI: 1.04–3.61, P = 0.038) versus nondrinkers. Additionally, smoking and higher Child–Pugh score marginally associated with HCC mortality at significance levels of P = 0.042 and P = 0.041, respectively. TACE combination therapy exhibited lower risk on HCC specific mortality than those treated by TACE monotherapy group (HR: 0.45, 95% CI: 0.26–0.82, P = 0.009) among all patients receiving these therapies. Hypothyroidism was inversely related to HCC mortality among the TACE combination patients' group (HR: 0.30, 95% CI: 0.13–0.68, P = 0.04). The result becomes more pronounced in HCCs also administered by TKIs and ICIs (HR: 0.14, 95% CI: 0.03–0.60, P = 0.009). Treatment-induced hypothyroidism is prevalent among HCC patients receiving TACE combined with TKIs/ICIs and is associated with improved survival, potentially reflecting immune activation. Further multinational studies are warranted to validate these observations across diverse ethnic populations and treatment protocols.

Keywords Hypothyroidism · Hepatocellular carcinoma · Transarterial chemoembolization · Tyrosine kinase inhibitors · Immune checkpoint inhibitors

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It usually comes from long-term liver problems caused by infections, drinking, or fatty

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liver disease. The major genetic modification during HCC development includes mitogen-activated protein kinase (MAPK) and vascular endothelial growth factor (VEGF) signaling hyperactivation [1], evading apoptosis and immune escape, such as upregulation of programmed death-ligand 1 (PD-L1) [2], which are related to tumor initiation and therapeutic responses, thus shaping the current treatment management.

Early stage HCC usually received surgical resection or radiofrequency ablation (RFA), while intermediate stage HCC received transarterial chemoembolization (TACE) [3, 4]. For advanced HCC, some systemic therapies including tyrosine kinase inhibitors (TKIs: sorafenib, lenvatinib) and immune checkpoint inhibitors (ICIs: nivolumab, pembrolizumab) were approved and became mainstays of practice for improving survival [5, 6]. However, these therapies could lead to thyroid dysfunction, especially hypothyroidism [7, 8]. Different studies showed varying incidence rates of hypothyroidism among patients with advanced HCC receiving TKI or ICI monotherapy [9–12]. Consequently, close monitoring of TH functions should be done routinely.

Functionally, thyroid hormones (THs) maintain cellular metabolic equilibrium in hepatocytes, regulate lipid metabolism, and even prevent carcinogenesis. However, it has been shown that the THs can also activate pro-tumorigenic pathways including MAPK and VEGF, and promote tumor growth [13]. Mechanistically, hypothyroidism resulted from TACE may come from the damage of thyrocytes caused by iodinated contrast used in imaging diagnosis, or transient ischemic harm inflicted on thyrocytes when the hepatic artery being blocked during the procedure [14]. TKIs mainly target TH synthesis by inhibiting VEGF receptors, and resulting in disordered thyroid vasculature and capillary regressing like the Wolff-Chaikoff effect [15]. Immune-mediated thyroiditis occurs through anti-PD-1 antibodies and cytotoxic T lymphocyte antigen 4 causing T cell invasion and autoimmune response to endocrine glands, namely ICIs [2].

Some aspects of the relationship between TH suppression, such as seen with treatment-induced hypothyroidism, and outcomes related to survival for HCC patients have been described by researchers in clinical settings [16–19]. Some studies propose that TH suppression associated with hypothyroidism may slow tumor growth, leading to favorable outcomes, while other clinicians attributed the poor outcomes to hypothyroidism induced by autoimmune driven toxicities [15]. Most of these inconsistent findings can be explained by different TKI/ICI treatments and the differences in the timing of thyroid dysfunction onset or resolution relative to treatment initiation. In light of these uncertainties and the substantial implications of hypothyroidism for patients, our study endeavors to elucidate the significance of treatment-induced hypothyroidism on HCC within a real-world setting, thereby bridging the existing knowledge gap.

Materials and methods

Patients

We retrospectively analyzed the clinical significance of treatment-induced hypothyroidism in patients who were treated with TACE alone or TACE combination therapy (TACE + TKIs and TACE + TKIs + ICIs) between March 23, 2023, and September 19, 2023. The patients were observed until the time of death, or at intervals of every half year.

Patients included: (1) aged 18 years or older at HCC diagnosis; (2) diagnosed with HCC; (3) treated with TACE alone or TACE-based combination therapy; and (4) possessing complete baseline thyroid function measurements. Patients excluded: (1) pre-existing severe thyroid disorders; (2) concurrent with other malignancies; (3) incomplete follow-up documentation.

Our study was approved by the First Hospital of Jilin University's Clinical Research Ethics Committee under the Clinical Research Ethics Committee (2024–686), and informed consent was obtained.

Thyroid function evaluation

According to the results of thyroid functions test, the definition of hypothyroidism was based on the recommendations of the American Thyroid Association and the European Thyroid Association. Primary subclinical or overt hypothyroidism patients have a serum thyroid-stimulating hormone (TSH) value exceeding the upper limit of the normal range while thyroid free tetraiodothyronine (FT4) are in accordance or reduced [20–22]. Besides thyroid functions, thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) were tested, because their abnormal increase could be very important during the onset and progress of hypothyroidism. The standard measurement ranges for THs used in this assay were: TSH in serum was between 0.35 and 4.94 uIU/mL, FT4 was between 9.01 and 19.05 pmol/L, TgAb was between 0 and 4.11 IU/mL, and TPOAb was between 0 and 5.61 IU/mL. Test reagents were chemiluminescent immunoassay reagents which were performed automatically by Abbott instruments (USA).

^{131}I uptake test

A month before the test, patients were instructed to avoid iodine-rich foods and medications. They fasted for 4 hours (h) before getting a small dose of ^{131}I (74 kBq).

When measured on-site, the patient sat and exposed the neck. The probe was positioned over the thyroid gland for 1-min counts, with background radiation subtracted. Our laboratory's reference ranges are 10–20% and 20–30% for the 2 h and 4 h ^{131}I uptake test, respectively.

Outcomes

Major outcomes were frequency and natural history of hypothyroidism after treatment. OS was calculated from the start of treatment (TACE alone or TACE combination therapy) until death from any cause.

Statistical analysis

All analysis was conducted using SPSS (v22.0; Inc., Chicago, IL) and GraphPad Prism (v8.0; Inc., La Jolla, CA). Continuous variables were expressed as mean ± SD or median with interquartile range (IQR), depending on whether it follows a normal distribution or not. Group comparison of continuous variables was carried out by unpaired T-test after checking if each variable meets the conditions for each test (normality and homogeneity of variance) through its corresponding test. Categorical data were presented as number and percentage (%), and analyzed by Chi-squared test or Fisher's exact test when applicable. Survival curves were assessed by Kaplan–Meier curve and compared by Log-rank Test. Confounders were adjusted in multivariate Cox Proportional Hazards Regression Model. Two-sided p values less than 0.05 was considered statistically significant.

Results

Study population

A total of 142 HCC patients from the general population were included in the real-world analysis based on undergoing a routine thyroid function test and having at least one session of TACE or TACE-based combination therapy. After excluding 2 patients with severe effects of Graves' disease, 5 cases complicated by malignancy, and 5 subjects without detailed follow-up documents, we ultimately selected 130 subjects for our study (50 cases under TACE alone and 80 under TACE combination therapy): among which, 39 cases treated with TACE combined with TKIs (31 with lenvatinib, 4 with apatinib, and 4 with sorafenib), and 41 cases treated with TACE combined with TKIs and ICIs (26 with lenvatinib + camrelizumab, 4 with lenvatinib + sintilimab, 2 with lenvatinib + tislelizumab, 1 with lenvatinib + atezolizumab, 1 with lenvatinib + pembrolizumab, 1 with lenvatinib + adebrelimab; 4 with sorafenib + camrelizumab, 2 with sorafenib + adebelimab). The baseline characteristics of the 52 cases with hypothyroidism compared to the 78 cases without hypothyroidism are summarized in Table 1.

Frequency and presentation of hypothyroidism

The median follow-up period was 28 months. Among the 50 patients undergoing TACE treatment, 11 patients (22.0%) developed hypothyroidism; among the 80 patients undergoing TACE combination therapy, 41 patients (51.3%) developed hypothyroidism (Fig. 1A).

Thyroid antibody testing

The baseline TPOAb levels were normal in 123 patients before treatment. There were 49 of them developed hypothyroidism after treated. Among all the patients with normal TPOAb levels before treatment, their TPOAb levels changed from normal to high in only 7 of them, of which there were 3 developed hypothyroidism after treated. As for TgAb value, the baseline TgAb levels were normal in 119 patients before treatment. There were 47 of them became hypothyroidism after treated. Among all the patients with normal TgAb levels before treatment, their TgAb levels changed from normal to high in 11 of them, of which there were only 5 developed hypothyroidism after treated. Among the patients with available follow-up data, 55 patients showed an increase in TPOAb levels (mean increase: 2.13 IU/mL), and 38 patients showed an increase in TgAb levels (mean increase: 8.26 IU/mL).

^{131}I uptake test

The baseline ^{131}I uptake was declined in 126 patients before treatment, of whom 51 developed hypothyroidism. In contrast, ^{131}I uptake were normal in 4 patients before treatment, of whom 1 developed hypothyroidism after TACE. ^{131}I uptake was reexamined in 12 patients in the follow-up period, all of whom showed decreased uptake. The mean ^{131}I uptake at 2 h and 4 h were decreased from 4.05% (the baseline value) to 3.19% (last follow-up), and from 5.30 to 4.25%, respectively.

Overall survival and mortality risk

Mortality rate in the whole study population was 25% (13/52) in patients with hypothyroidism vs. 48.7% (38/78) in patients without hypothyroidism (P = 0.007). Mortality rates between patients with hypothyroidism receiving TACE monotherapy and those without hypothyroidism showed no difference (36.4% [4/11] vs. 53.8% [21/39], respectively; P = 0.306). But for mortality rate in TACE combined

Table 1 Clinical characteristics of all patients with or without hypothyroidism

Variables	All	Hypothyroidism	Without hypothyroidism	P value
Age (SD), years	61.78 ± 8.80	61.04 ± 8.46	62.27 ± 9.03	0.437
Gender, n (%)				0.338
Male	102	43	59	
Female	28	9	19	
Smoking, n (%)				0.767
Yes	48	20	28	
No	82	32	50	
Drinking, n (%)				0.742
Yes	33	14	19	
No	97	38	59	
Hepatitis virus, n (%)				0.138
Hepatitis B	84	37	47	
Hepatitis C	17	8	9	
No	29	7	22	
ECOG PS, n (%)				0.000
0	61	23	38	
1	54	24	30	
2	12	5	7	
3	3	0	3	
Portal infiltration, n (%)				0.596
Yes	44	19	25	
No	86	33	53	
Hepatic venous infiltration, n (%)				0.502
Yes	10	5	5	
No	120	47	73	
AFP, ng/mL	14745.56 ± 34540.35	15538.37 ± 35511.14	14217.04 ± 34099.56	0.832
Child–Pugh status, n (%)				0.123
A	49	25	24	
B	45	14	31	
C	36	13	23	
BCLC stage, n (%)				
B	33	10	23	
C	57	28	29	
D	40	14	26	
Prior operation, n (%)				0.874
Yes	7	3	4	
No	123	49	74	
Prior TACE, n (%)				0.147
Yes	4	3	1	
No	126	49	77	

ECOG PS: Eastern Cooperative Oncology Group Performance Status; AFP: Alpha-Feto protein; BCLC:Barcelona Clinic Liver Cancer; TACE: transarterial chemoembolization

therapy, 22% (9/41) in patients with hypothyroidism were less than 43.6% (17/39) in patients without hypothyroidism (P = 0.039); while for TACE + TKIs therapy, the mortality rate among patients with hypothyroidism was 31.3% (5/16), which had not shown a difference from that in patients without hypothyroidism with a proportion of 64.3% (9/23) (P = 0.614). When using TACE combined with TKIs and ICIs, the mortality rate of patients with hypothyroidism were less than that of patients without hypothyroidism (16% [4/25] vs. 50% [8/16], respectively; P = 0.02) (Fig. 1B).

For entire cohort, the median OS cutoff in patients with hypothyroidism reached 37.5 months, and median OS

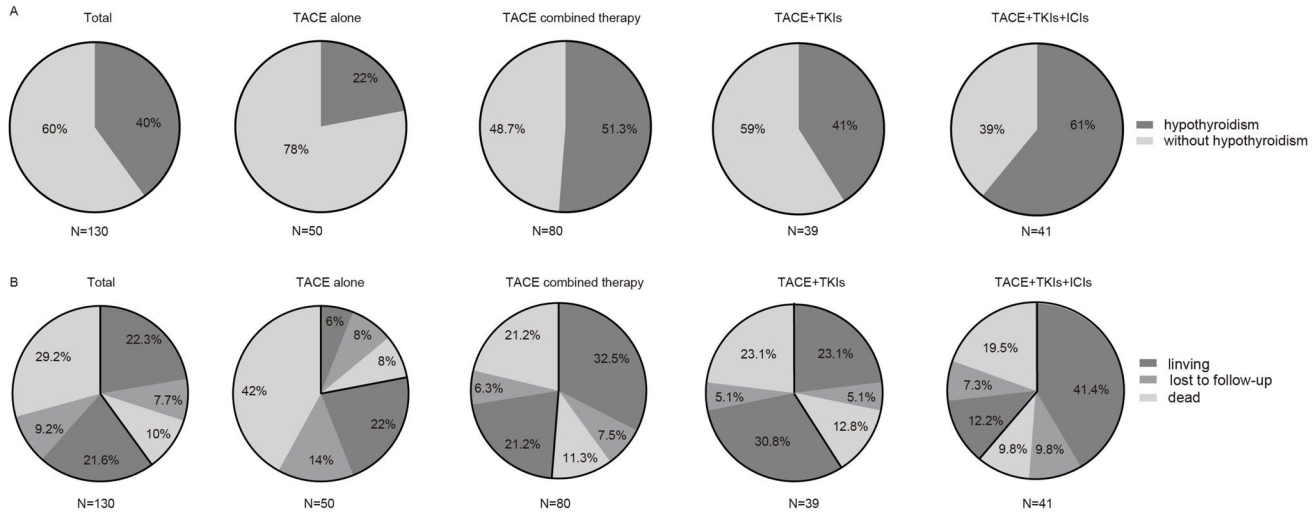

Fig. 1 Distribution of thyroid function and survival of HCC patients after treatment. (**A**) Proportion of hypothyroidism. (**B**) Proportion of mortality rates

was 23.33 months in patients without hypothyroidism. There was a significant statistical difference between them (P = 0.015). For patients treated with TACE alone, there was no difference between the median OS of patients with hypothyroidism and those of participants without hypothyroidism (P = 0.864). For patients treated with TACE combination therapy, the median OS cutoff in patients with hypothyroidism reached 37.5 months, and median OS was 28.42 months in patients without hypothyroidism. There was a significant statistical difference between them (P = 0.036). For patients treated with TACE combined with TKIs, there was no difference between the median OS of patients with hypothyroidism and those of participants without hypothyroidism (P = 0.060). For patients treated with TACE combined with TKIs + ICIs, the median OS cutoff in patients with hypothyroidism was not reached. But it was longer than those without hypothyroidism where median OS was 22.54 months (P = 0.005) (Fig. 2).

In univariate and multivariate analysis, cancer-specific mortality correlated with some factors including sex, drinking, and hypothyroidism in the whole population as well as subgroups received TACE alone or combination. In all patients, after adjustment for confounding factors, drinking showed an increased risk of HCC mortality (HR: 1.94, 95% CI: 1.04–3.61, P = 0.038) versus nondrinkers. Additionally, smoking and higher Child–Pugh score marginally associated with HCC mortality at significance levels of P = 0.042 and P = 0.041, respectively. TACE combination therapy exhibited lower risk on HCC specific mortality than those treated by TACE monotherapy group

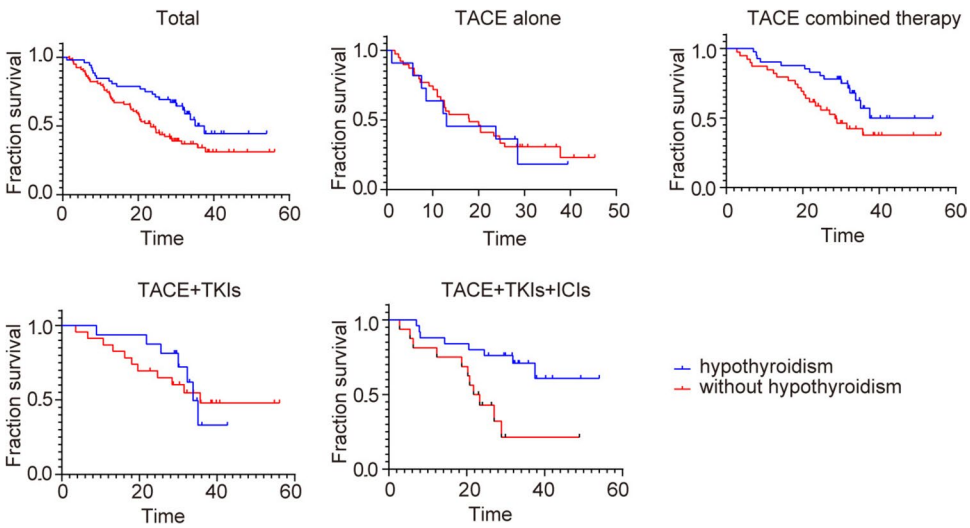

Fig. 2 Kaplan–Meier survival curves showing comparison of overall survival between HCC patients with and without hypothyroidism after treatment

(HR: 0.45, 95% CI: 0.26–0.82, P = 0.009) among all patients receiving these therapies. Within the TACE monotherapy subgroup, drinkers developed a notable increase risk on HCC mortality compared to nondrinkers (HR: 5.82, 95% CI: 1.78–19.02, P = 0.004). Hypothyroidism was inversely related to HCC mortality among the TACE combination patients' group (HR: 0.30, 95% CI: 0.13–0.68, P = 0.04). The results were more pronounced in HCCs treated with TACE + TKIs + ICIs, which indicates that hypothyroidism had a strong correlation with decreased HCC mortality rate among the proportion in above treatment modality's (HR: 0.14, 95% CI: 0.03–0.60, P = 0.009) (Table 2 and Supplementary Table 1).

Discussion

Our study provides valuable insights into the relationship between hypothyroidism and outcomes in patients with HCC undergoing TACE alone or in combination with TKIs and/or ICIs. The findings highlight the potential impact of hypothyroidism on OS and mortality risk in this patient population.

We found a much higher incidence of hypothyroidism (51.3%) among combination therapy recipients than those who received TACE alone (22.0%), indicating combining TACE + TKI/ICI therapies increases the risk of hypothyroidism. Interestingly, in these combined-therapy users, more developed hypothyroidism if treated with TACE + TKIs + ICIs instead of TACE + TKIs. These differences were probably caused by time-related changes. In fact, Shao et al. [17]. reported 20% incidence of hypothyroidism following sorafenib monotherapy in HCC patients with advanced disease, while Wu et al. [9]. reported 47.7% incidence of hypothyroidism after treatment with sintilimab/camrelizumab. When compared to early investigations based on single-agent TKI or ICI treatment, our current study shows a higher incidence of hypothyroidism, which might also be explained by the synergistic or additive immunomodulatory effects of combination therapy.

In terms of the available literature on hypothyroidism and HCC survival, it can be clearly seen that there are many differences in the final result due to different research methods. For instance, Shao et al. [17]. found that among advanced HCC patients treated with sorafenib, hypothyroidism was significantly associated with age > 65 years, higher serum Alpha-Feto protein level (> 400 ng/mL), and poor OS; whereas Xu et al. [23]. demonstrated that hypothyroidism resulted in a longer progression free survival (PFS) (7.44 vs. 5.68 months, P = 0.006) for HCC patients receiving anti-PD-1 therapy, which was similar with evidence revealing that hypothyroidism after atezolizumab and bevacizumab gave rise to longer PFS, OS, and objective response rate-in contrast to non-hypothyroidism [24]. Therefore, the complicated relationship between hypothyroidism and HCC should be further investigated using several influence factors. In our current work, we explored the influence of TACE alone or combination treatment on hypothyroidism and survival, providing a broader view about hypothyroidism influencing treatment response for HCC. The univariate analysis and multivariate analysis both revealed that gender, drinking history, and hypothyroidism were related to HCC mortality. Although drinking correlated with higher mortality risk across all treatments, hypothyroidism tended toward lower mortality in the TACE combination treatment group, especially in TACE + TKI + ICI subgroups, corresponding to results reported in previous studies showing that immune-related adverse events including hypothyroidism predicted good outcomes in ICI recipients.

ICIs trigger the immune system against tumor cells [25]. This immune response is useful for attacking cancer cells, but may unexpectedly interact with healthy tissues and, in particular, the thyroid gland. Sometimes it can provoke an autoimmune reaction on the thyroid tissue and cause autoimmunity related to ICI treatment: this can lead to hypothyroidism because of immune-related side effects [26]. At other times it causes antibodies production against the thyroid, leading to the dysfunction of the gland because of impaired thyroid functions and hormone production. It may also induce the secretion of inflammatory cytokines in the thyroid and activate immune cells, therefore causing disruption of its normal functioning. Specific ICIs, especially PD-1/PD-L1 antibodies, may induce cytotoxic CD4 memory T cell activation, destroying thyroid follicular cells, decreasing hormones level and inducing release of pro-inflammatory cytokines [27]. TKIs act on several intracellular signaling pathways that are crucial for the synthesis of hormones produced by the thyroid [11, 28, 29], and could impair the transport of thyroids circulating in the blood stream [30]. TKIs may interfere with signaling pathways involved in the synthesis of thyroid hormones. Certain TKIs can affect the transport of thyroid hormones within the bloodstream, leading to altered bioavailability and reduced levels of active hormone [31], diminishing active hormone concentrations. Furthermore specific TKIs might trigger direct cytotoxicity on the thyroid follicular cells, causing hormone depletion and damage to the gland. Thus, combining ICI and TKI will probably augment their combined immunologic effect on the body, damaging thyroid function in different manners.

TgAb and TPOAb could predict those who developed thyroid dysfunction following ICIs treatment, suggesting that these autoantibodies might become a potential biomarker of thyroid dysfunction. The baseline positivity

Table 2 Multivariable analysis of factors associated with OS in HCC patients

Variables	Total		TACE alone		TACE + TKIs and TACE + TKIs + ICIs		TACE + TKIs + ICIs	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Age, years								
< 60	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
≥ 60	1.03 (0.60–1.76)	0.923	1.27 (0.57–2.83)	0.556	1.16 (0.53–2.57)	0.706	1.19 (0.29–4.74)	0.818
Gender								
Male	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Female	1.17 (0.61–2.26)	0.634	0.41 (0.14–1.19)	0.101	1.72 (0.57–5.22)	0.338	2.42 (0.25–23.62)	0.448
Smoking								
No	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	0.52 (0.28–0.98)	0.042	0.64 (0.20–2.03)	0.449	0.16 (0.05–0.47)	0.001	0.17 (0.03–0.99)	0.049
Drinking								
No	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	1.94 (1.04–3.61)	0.038	5.82 (1.78–19.02)	0.004	1.96 (0.70–5.48)	0.201	0.77 (0.10–5.78)	0.797
Hepatitis virus								
No			1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Hepatitis B	1.12 (0.58–2.17)	0.736	2.90 (1.08–7.74)	0.034	0.64 (0.22–1.90)	0.420	0.77 (0.10–6.06)	0.807
Hepatitis C	0.88 (0.32–2.43)	0.804	0.27 (0.03–2.81)	0.271	0.76 (0.18–3.15)	0.702	0.04 (0.04–11.39)	0.762
ECOG PS								
0	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)			
1	1.25 (0.66–2.37)	0.497	0.36 (0.10–1.27)	0.113	1.78 (0.68–4.63)	0.237	3.20 (0.66–15.49)	0.149
2	1.00 (0.41–2.45)	0.998	0.24 (0.63–0.94)	0.041	11.32 (2.26–56.85)	0.003	21.1 1(0.60–742.22)	0.093
3	1.41 (0.28–7.09)	0.681	–	–	1.32 (0.20–8.80)	0.775	9.83 (0.24–407.24)	0.229
Portal infiltration								
No	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	1.40 (0.76–2.58)	0.275	2.29 (0.82–6.34)	0.113	1.57 (0.61–4.00)	0.35	0.78 (0.13–4.66)	0.786
Hepatic venous infiltration								
No	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	0.99 (0.39–2.57)	0.998	2.20 (0.27–17.79)	0.459	0.66 (0.12–3.66)	0.634	4.64 (0.19–114.03)	0.348
AFP, ng/mL								
≤ 300	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
> 300	1.53 (0.87–2.71)	0.140	1.08 (0.35–3.39)	0.890	1.28 (0.58–2.84)	0.536	2.05 (0.35–12.04)	0.427
Child–Pugh status								
A	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
B	1.18 (0.58–2.41)	0.649	7.43 (1.27–43.62)	0.026	1.04 (0.38–2.51)	0.936	0.23 (0.05–1.08)	0.063
C	6.31 (1.08–37.08)	0.041	14.82 (0.68–322.38)	0.086	3.90 (0.48–31.69)	0.203	0.22 (0.00–28.28)	0.537
BCLC stage								
B	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
C	0.97 (0.51–1.86)	0.934	0.26 (0.08–0.86)	0.027	0.97 (0.37–2.51)	0.941	3.21 (0.46–22.41)	0.239
D	0.25 (0.04–1.49)	0.128	0.10 (0.00–2.14)	0.140	0.22 (0.03–1.71)	0.147	0.53 (0.028–10.02)	0.67
Prior operation								
No	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Yes	0.62 (0.18–2.14)	0.453	1.07 (0.11–10.10)	0.953	1.18 (0.22–6.42)	0.847	8.52 (0.10–733.28)	0.346
Thyroid function								
Without hypothyroidism	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
With hypothyroidism	0.62 (0.34–1.15)	0.129	0.92 (0.33–2.54)	0.872	0.30 (0.13–0.68)	0.04	0.14 (0.03–0.60)	0.009
Treatment method								
TACE alone	1.0 (Ref)		–		–		–	
TACE combined	0.45 (0.26–0.82)	0.009	–	–	–	–	–	–

OS: overall survival; HCC: hepatocellular carcinoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; BCLC:Barcelona Clinic Liver Cancer; TACE: transarterial chemoembolization; TKIs: therapies (tyrosine kinase inhibitors; ICIs: immune checkpoint inhibitors; AFP: Alpha-Feto protein

of both TgAb and TPOAb stratifies the risk of developing thyrotoxicosis or hypothyroidism after ICI treatment more precisely, enabling us to tailor cancer care measures for each individual patient [23]. There was no difference in the levels of autoantibodies between HCC patients with hypothyroidism and those without in our study, so some discrepancy might be attributed to the difference in criteria used for diagnosing hypothyroidism among different studies. The levels of TPOAb and TgAb increased dramatically during follow-up periods, especially in subjects with hypothyroidism. ^{131}I uptake test results also confirmed this finding. Although similar baseline ^{131}I uptake value existed between patients with and without hypothyroidism, there was a decrease upon follow-up; however, the exact influence on hypothyroidism could not be determined due to too few evaluated patients receiving repeat testing. In addition, the baseline ^{131}I uptake value decreased almost in every subject compared with normal values, suggesting that ^{131}I uptake might have better sensitivity than serum TSH in detecting hypothyroidism and should be further explored.

Our article contributes to the existing literatures from three aspects: First, our study focuses on a real-world cohort of HCC patients instead of selected samples from highly specialized populations. Second, it is the first article assessing the long-term impact of hypothyroidism on survival outcomes in HCC patients undergoing TACE, TKIs and ICIs. By integrating impacts of three kinds of therapies, we provide profound understanding of the complex relationship between ICI-induced hypothyroidism and liver cancer prognosis. Third, we carefully assessed the thyroid function using multiple thyroid functions tests and ^{131}I uptake, permitting precise diagnosis of hypothyroidism and its subgroups, which is an improvement compared to prior works.

Also, there are limitations to our study. First, because this is a retrospective study, the actual incidence of treatment-related hypothyroidism may be underestimated; there was no uniformity in evaluating thyroid function tests and radioactive iodine uptake at the time of HCC diagnosis or during follow-up examinations. If uniform evaluation is not achieved, it will cause underestimation of subclinical hypothyroidism, making it difficult to determine the extent of abnormal endocrine function of thyroid tissue caused by liver cancer and timely initiation of hormone replacement therapy if necessary. Second, due to fewer cases, the results as predictors for the whole group of HCC patients need to be confirmed by more representative large-sample studies with multivariant data collected from multiple centers. The current results should be regarded as preliminary ones that require validation in prospective cohort studies before being applied clinically. Third, different treatments among subjects involved influenced some analytical parameters, thus leading to unreliable results. However, we still get beneficial information about real-world practice concerning management of HCC and ideas worth further exploration in this context. Further work has to be done on more homogeneous sets of individuals submitted to standardized therapies, using proper statistical tools for controlling bias factors. Fourth, the ethnic group studied is not wide enough and cannot represent all races, although one can assume that related biological mechanisms between liver cancer and races apply universally. More extensive investigation involving varied ethnic groups is needed to evaluate whether these results will extend to other races or need adjustment based on each specific ethnicity. Fifth, because the study could not monitor changes in hormone levels after hormone replacement therapy, no conclusions about the effect of hormone replacement therapy on clinical outcome for patients treated with TACE plus TKIs and ICIs could be drawn.

In conclusion, the present real-world clinical study suggests that hypothyroidism is commonly met in HCC patients who received TACE combined with TKIs and ICIs. Hypothyroidism correlated better with improved OS and lower mortality than without hypothyroidism, suggesting the possible benefit of hypothyroidism monitoring on response of ICIs. Further research efforts regarding the application of hypothyroidism as a marker of ICI efficacy are warranted.

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Data availability The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Competing interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval This study was approved by the Ethics Committee of the First Hospital of Jilin University (2024–686).

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