ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
August 2025; 24(4):462-471.
DOI:10.18502/ijaai.v24i4.19127

Predictive Value of Peripheral Blood Follicular Helper T Cells for Short-term Prognosis in Patients with Hepatocellular Carcinoma Treated with Immune Checkpoint Inhibitors

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Received: 21 October 2024; Received in revised form: 17 December 2024; Accepted: 14 January 2025

ABSTRACT

Peripheral blood follicular helper T cells (Tfh) are essential in humoral immunity; however, their prognostic significance in hepatocellular carcinoma (HCC) patients treated with immune checkpoint inhibitors (ICIs) is not well understood. This study aimed to evaluate the predictive value of Tfh cells for short-term prognosis in 200 HCC patients undergoing ICIs.

A retrospective analysis categorized patients based on their clinical outcomes at six months post-treatment: those demonstrating improvement were classified as having a favorable prognosis (n=86), while those with no remission, deterioration, or death were classified as having a poor prognosis (n=114). Key prognostic factors assessed included C-reactive protein (CRP), interleukin-6 (IL-6), Tfh cell counts, and combination therapy.

Significant associations were identified between prognosis and CRP, IL-6, Tfh cell counts, and combination therapy. Multivariate analysis revealed these factors as independent predictors of short-term prognosis, explaining 78.3% of the variance. The area under the curve (AUC) for Tfh cells was 0.902 (95% CI: 0.8567-0.9477), with 100% sensitivity and 80.70% specificity at a cut-off of 1.995. Patients with elevated Tfh levels (≥1.995, n=93) had a median overall survival (OS) of 5 months, significantly earlier than those with lower levels (<1.995, n=107), whose median OS was not reached.

Tfh cells are independent predictors of short-term prognosis in HCC patients receiving ICIs. Reduced Tfh levels correlate with improved outcomes, providing crucial insights for clinical decision-making.

Keywords: Hepatocellular carcinoma; Immune checkpoint inhibitor; Peripheral blood follicular helper T cells; Predictive value; Short-term prognosis

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INTRODUCTION

Immune checkpoint inhibitors (ICIs), as an emerging immunotherapy, have shown great potential in improving the prognosis of patients.[1] However, there is

statistically significant heterogeneity in the response of different patients to ICIs treatment, with some patients achieving statistically significant efficacy while others may have limited efficacy or even adverse reactions.[2-3] Therefore, accurately predicting patients' responses to ICIs treatment and optimizing therapeutic strategies have become an important research direction in the current field of hepatocellular carcinoma (HCC) treatment.[4-5]

Peripheral blood follicular helper T cells (Tfh), as a specialized T cell subset, Tfh cells play a pivotal role in humoral immunity.[6] They are not only involved in B cell activation and antibody production, but they also play a key role in modulating the intensity and duration of immune responses.[7] The further study of Tfh cells, has led to a gradual realization of theirpotential role in tumor immunity. This realization is particularly relevant in malignant tumors such as HCC, where the number and functional status of Tfh cells may be closely related to the prognosis of patients.[8-9] In the context of ICIs therapy, Tfh cells may have an important impact on the short-term prognosis of HCC patients by affecting the function of B cells and regulating the humoral immune response. However, the specific role of Tfh cells in predicting the efficacy of ICIs in HCC patients remains to be fully elucidated.[10] Further investigations are needed to determine the prognostic value of Tfh cells in this context.

This study aims to assess the prognostic potential of peripheral Tfh cells in HCC patients undergoing ICIs treatment. We hypothesize that high peripheral Tfh cell levels are associated with improved short-term prognosis in these patients. The findings of this study will provide valuable insights into the role of Tfh cells in ICI therapy and may contribute to the development of novel prognostic biomarkers for HCC patients receiving ICIs.

MATERIALS AND METHODS

Research subjects

200 patients treated with ICIs for HCC in The First Affiliated Hospital of Fujian Medical University from Jan 2020 to 2023 were retrospectively selected as the study subjects. Inclusion criteria: (1) Histologically confirmed HCC diagnosis. (2) Expected survival of ≥ 3 months. (3) Complete clinical data available. (4) Patients must not have received other therapeutic interventions before ICIs treatment. (5) Patients with Barcelona Clinic Liver Cancer (BCLC) stage B or C. Exclusion criteria: (1) History of other malignant tumors. (2) Chronic infection. (3) Loss to follow-up.

Methods

The last follow-up for this studywas until January 2024. Patients were divided into a favorable prognosis group (n=86) and a poor prognosis group (n=114) according to their short-term prognosis. Prognosis criteria: If the patient's condition is relieved or significantly improved within six months after treatment, the prognosis is considered favorable; if the patient's condition is not remitted, worsened or died within six months after treatment, the prognosis is considered poor. Overall survival (OS) is defined as the time from the start of treatment to the patient's last follow-up or death.

Detection of Peripheral Blood Lymphocyte Subsets and Cytokines

This study used flow cytometry (BD FACS Aria III, BD, USA) to analyze peripheral blood lymphocyte subsets and cytokines. Lymphocyte subsets were detected using fluorescently labeled antibodies (CD3, CD8, CD45, CD4, CD16, CD56, CD19) (Beckman Coulter, USA). Plasma cytokine levels were measured using a multiplex microsphere flow immunoassay.

Sample Collection and Pretreatment

2 mL EDTA anticoagulated blood, divided into two tubes. Tube 1: Test lymphocyte subsets at room temperature (25℃) within 6 hours, or store at 4℃ and test within 48 hours. Tube 2: Separate plasma (1000×g, 10 minutes) within 4 hours, store at -20℃ and test within 48 hours, avoid repeated freezing and thawing.

(2) Experimental Procedure

Lymphocyte Subset Detection

A total of 20 μL of reagent is added to a counting tube, followed by the introduction of 50 μL of blood sample, mixing thoroughly. The mixture is then incubated at room temperature in the dark for 15 minutes. Afterward, 450 μL of diluted hemolysin is added, mixed well, and incubated in the dark for an additional 15 minutes. The sample is subsequently analyzed using flow cytometry, with analysis software employed to determine both percentage and absolute counts of lymphocyte subsets.

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Cytokine Detection

To a flow tube, sequential additions of 25 μL of buffer, capture microsphere antibody, detection antibody, and plasma (or calibrator) are made. The mixture is incubated at room temperature in the dark for 2 hours while shaking at 300 rpm. Following this, 25 μL of labeled streptavidin is added, and incubation continues for 30 minutes. Subsequently, 1 mL of diluted wash buffer is added, mixed thoroughly, and the sample is centrifuged at 300×g for 5 minutes, discarding the supernatant. Finally, 120 μL of diluted wash buffer is added to resuspend the sample. The sample is analyzed via flow cytometry, with analysis software utilized to quantify plasma cytokine levels.

Detection Methods for Serum Indicators

Biochemical analysis was used to detect C-reactive protein (CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). Flow cytometry was used to detect the percentage of Tfh cells. ELISA was used to detect interleukin-6 (IL-6) (PI330, Beyotime Biotechnology) and tumor necrosis factor alpha (TNF-α) (97072ES96, Shanghai Yeasen Biotechnology Co., Ltd.).

Treatment Regimens for Liver Cancer and Related Evaluation Indicators

All treatment protocols in this study were conducted in accordance with the “Chinese Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition)”. In clinical trials, the research team used lenvatinib (Emotiai Europe Ltd./ The combination therapy produced by Taitai Europe Co., Ltd.) and triplimumab (jointly developed by Suzhou Zhonghe Biomedical Technology Co., Ltd. and participated by Shanghai Junshi Biomedical Technology Co., Ltd.) to target specific diseases. The dose of lenvatinib is adjusted individually based on the patient's weight: 8mg per day for patients weighing less than 60kg; 16mg per day for patients weighing≥60 kg. Triplimumab was calculated at 3mg per kilogram of body weight and given intravenously every three weeks until intolerance or disease progression occurred. Combination therapy aims to improve efficacy and delay the course of disease through synergy of drugs. Patients were followed up regularly every three months after starting treatment. During each follow-up visit, physical examinations, blood tests (including liver function, tumor markers, etc.), and imaging examinations (such as ultrasound, CT, or MRI) were performed to assess treatment response, disease progression, and any treatment-related adverse events.

Efficacy Judgment Criteria

Complete response (CR): This criterion is defined as the complete disappearance of arterial enhancement in the target tumor lesion after treatment, or the complete cessation of tumor activity, achieving clinical and radiologically tumor-free status. Partial Response (PR): refers to a significant decrease in living residual cancer tissue in the tumor lesion compared with the baseline level, and the specific reaching or exceeding 30%. This improvement needs to be confirmed by imaging and meets the requirements of RECIST criteria. Progressive disease (PD): If during treatment, a 20% increase in tumorvolume and residual cancer tissue compared with the baseline level is observed, or a new lesion appears, it is judged as disease progression. This criterion reflects the tumor's resistance to treatment and suggests that treatment options may need to be adjusted. Stable Disease (SD): When the change in the tumor lesion neither meets the PR reduction criterion nor the PD increase criterion, that is, when it is between PR and PD, the disease is judged to be stable. This means that the tumor has neither shrunk significantly nor worsened significantly under current treatment.

Based on the above criteria, the disease control rate (DCR) was further calculated. The calculation formula was: (number of CR cases + number of PR cases + number of SD cases) divided by the total number of cases, multiplied by 100%. DCR is an important indicator to measure the overall ability of a treatment plan to control disease and reflects the positive impact of treatment on a patient's condition.

See Table 1 for the efficacy of the two groups of patients.The curative effect in patients with poor prognosis was significantly lower than that in patients with good prognosis ($p<0.05$).

Statistical Analysis

Experimental data were analyzed using SPSS 27.0 and GraphPad Prism 9.1.0. Normally distributed metrics were reported as mean±SD andanalyzed with a t-test. Categorical data were presented as counts/rates and analyzed using $\chi 2$ or Fisher's exact test. Factors influencing outcomes were explored through logistic regression. ROC curves were used to assesse predictive power, with $p<0.05$ indicating statistical significance.

RESULTS

Prognosis of Patients Treated with ICIs for HCC

There was a statistically significant difference (p<0.05) in CRP, IL-6, Tfh cells combined with other anti-tumor treatments. See Table 2.

CRP, IL-6, Tfh cells, when combined with other anti-tumor treatments were used as independent variables, and the assignments are shown in Table 3. After the assignment, prognosis was used as the dependent variable for analysis (poor=1, good=0). The results of multiple linear regression analysis showed that CRP, IL-6 and Tfh cells in combination with other anti-tumor therapies were independent factors influencing the short-term prognosis of patients treated with HCC ICIs (p<0.05), explaining a 78.3% variation, as shown in Table 4.

Table 1. Observation of Efficacy in Patients with hepatocellular carcinoma Treated with immune checkpoint inhibitors

	Number of Patients	Complete Response	Partial Response	Progressive Disease	Stable Disease	Disease Control Rate (%)
Group with favorable prognosis	86	57	26	3	0	95.35
Poor prognosis group	114	32	30	30	22	73.68
Z/χ^2 value			Z=-5.511			4.306
p value			0.001			0.001

Table 2. Factors influencing the short-term prognosis of patients treated with immune checkpoint inhibitors for hepatocellular carcinoma

Baseline data		Group with favorable prognosis (n=86)	Poor prognosis group (n=114)	t/χ^2 value	p
Age (years)		65.13±6.70	66.70±7.14	1.583	0.115
Sex	Male	48	62	0.040	0.841
	Female	38	52		
BMI (kg/m2)		20.50±1.58	20.35±1.41	0.682	0.496
Smoking history	Yes	32	40	0.096	0.757
	No	54	74		
Drinking history	Yes	38	38	2.451	0.118
	No	48	76		
Hepatitis B infection	Yes	21	30	0.093	0.761
	No	65	84		
Type of HCC	Hepatocellular carcinoma	81	108	0.169	0.866
	Intrahepatic cholangiocarcinoma	5	6		
Combined with other antineoplastic therapies	Yes	8	30	9.220	0.002
	No	78	84		

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Table 2. Continued...

Baseline data		Group with favorable prognosis (n=86)	Poor prognosis group (n=114)	t/χ^2 value	*p*
Immunotherapy regimen	Monotherapy	83	107	0.852	0.394
	Combination therapy	3	7		
CRP (mg/L)		5.07±1.16	7.47±0.97	15.898	0.001
IL-6 (pg/L)		6.07±1.22	7.93±0.60	14.205	0.001
White blood cell count (×109/L)		6.47±0.83	6.50±0.84	0.287	0.775
Aspartate aminotransferase (U/L)		38.68±2.60	38.29±2.45	1.109	0.269
Tfh cells (%)		1.46±0.28	2.63±0.80	12.970	0.001
TNF-α (pg/mL)		1.40±0.06	1.41±0.07	1.063	0.289
Alanine aminotransferase (U/L)		37.06±1.86	36.90±1.79	0.607	0.544
Alkaline phosphatase (U/L)		97.78±1.56	97.54±1.53	1.103	0.271

Table 3. Assignment

Influencing factors	Assignment
CRP	Brought in by original value
IL-6	Brought in by original value
Tfh cells	Brought in by original value
Combined with other antineoplastic therapies	Yes=1, No=0

Table 4. Multiple linear regression analysis

Influencing factors	B	Standard error	Beta	t	Significance	95%CI
Constant	-0.524	0.097		-5.416	.001	-0.715~-0.333
CRP	0.181	0.037	0.171	4.913	.001	0.108~0.254
IL-6	0.122	0.013	0.391	9.442	.001	0.097~0.147
Tfh cells	0.128	0.016	0.336	8.272	.001	0.098~0.159
Combined with other antineoplastic therapies	0.158	0.024	0.272	6.674	.001	0.111~0.205

Note: R=0.887, R^2=0.787, adjusted R^2=0.783, p<0.001.

Tfh cells, CRP, IL-6, and Combination Therapy for Short-Term Prognosis

The area under the curve for Tfh cells in predicting short-term prognosis of patients treated with ICIs was 0.902, and the standard error was 0.023 (95% CI: 0.8567-0.9477), with a Youden index of 0.80. At this time, the sensitivity and specificity were 100% and 80.70% respectively; CRP was 0.960, standard error was 0.011 (95% CI: 0.9386-0.9803), with a Youden index of 0.78. the sensitivity was 100%, the specificity was 78.07%, IL-6 was 0.931, standard error was 0.016 (95% CI: 0.9009-0.9619), with a Youden index of 0.80. The sensitivity was 100%, the specificity was 78.07%, when combined with other anti-tumor treatments was 0.6991, standard error was 0.037 (95% CI: 0.6269-0.7713), with a Youden index of 0.80. The sensitivity was 49.12%, and the specificity was 90.70%, as shown in Figure 1, 2, 3 and 4.

Overall Survival Based on Tfh Cell Levels

According to the optimal cut-off value of Tfh cells for predicting poor prognosis in patients with HCC treated by ICIs, 200 patients were regrouped into high Tfh cell group (Tfh cells ≥1.995, n =93) and low Tfh cell group (Tfh cells <1.995, n=107). None of the 200 patients were lost to follow-up. The median OS was 5 months (95% CI: 3.911-9.409) in the high Tfh cell group and was not reached (95% CI: 0.1063-0.2557) in the low Tfh cell group, meaning that more than half of the individuals had not died by the end of the observation period. This finding indicated that patients had a better prognosis, and the difference was statistically significant (p<.05), as shown in Figure 5.

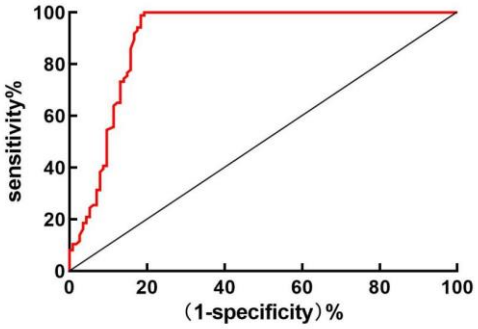

Figure 1. ROC curve of Tfh cells

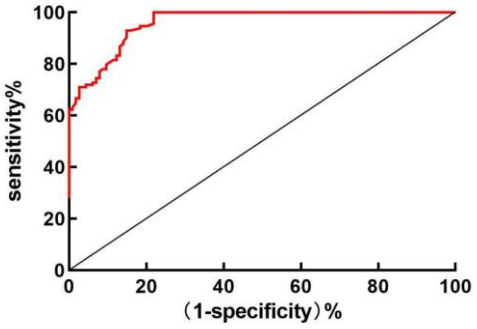

Figure 2. ROC curve of CRP

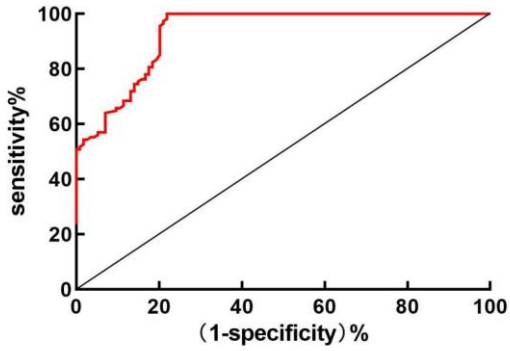

Figure 3. ROC curve of IL-6

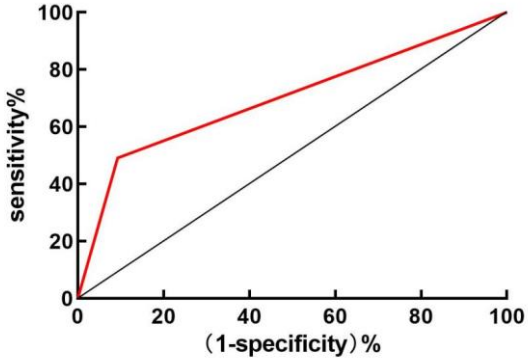

Figure 4. ROC curve in combination with other antineoplastic treatments

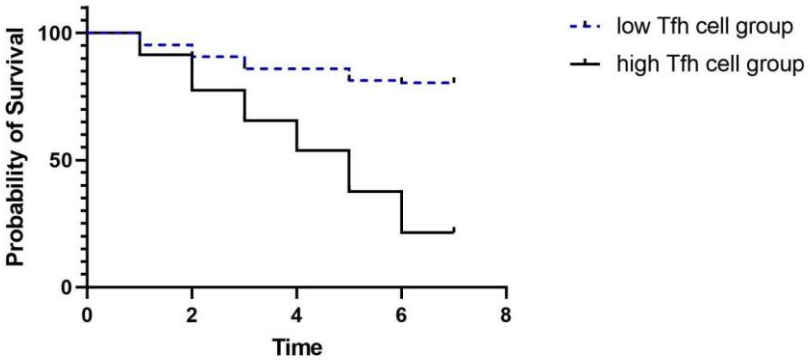

Figure 5. Survival curve

DISCUSSION

In the realm of HCC treatment, ICIs have emerged as a beacon of hope, offering new treatment avenues for numerous patients. However, although ICIs have achieved statistically significant efficacy in some patients, individual differences in their efficacy remain an issue that needs to be addressed.[11] This highlights the critical need to identify biomarkers capable of predicting ICI treatment response, ultimately enabling treatment optimization and improved outcomes. This study focused on peripheral blood follicular helper T cells and explored their predictive value in the short-term prognosis of patients with HCC receiving ICIs, providing a new perspective for research in this field.

Follicular helper T (Tfh) cells, a specialized subset of T cells, primarily reside in lymphoid follicles and are essential for B cell differentiation and antibody production.[12-13] Through cytokine secretion, costimulatory molecule expression, and the formation of stable immune synapses with B cells, Tfh cells orchestrate humoral immune responses by promoting B cell activation and antibody class switching.[14] Tfh cells' significance in autoimmune disorders, infections, and tumor immunity has been increasingly recognized through recent research advancements.[15-16] Within the tumor microenvironment, Tfh cells have garnered increasing attention due to their potential influence on tumor immunity. On the one hand, Tfh cells may contribute to enhancing the killing effect of humoral immunity on tumor cells by promoting B cell activation and antibody production. Within the tumor microenvironment, Tfh cells have garnered increasing attention due to their potential influence on tumor immunity.[17-18] Conversely, Tfh cells may also modulate the delicate balance within the tumor immune microenvironment through intricate interactions with other immune cells.[19] For instance, Tfh cells have been shown to enhance antitumor immunity by recruiting and activating CD8+ T cells and NK cells.[20-21] However, the precise mechanisms by which Tfh cells exert their effects in the context of ICI therapy for HCC remain to be fully elucidated, warranting further in-depth investigation.[22]

High Tfh cell levels independently predicted favorable short-term prognosis in HCC patients treated with ICIs. This finding aligns with the observed higher DCR in the favorable prognosis group (95.35%) compared to the poor prognosis group (73.68%). The study also identified CRP and IL-6 as independent predictors of short-term prognosis. This is noteworthy as Tfh cells are known to influence inflammatory responses. Elevated CRP and IL-6, both inflammatory markers, in the poor prognosis group suggest a possible link between Tfh cell function, systemic inflammation, and response to ICIs. Further investigation into the interplay between these factors could provide valuable insights into the underlying mechanisms. This finding is of significant clinical importance. First, it reveals the potential role of Tfh cells in the response to ICIs for HCC and provides new clues to understand individual differences in the efficacy of ICIs. Secondly, as a peripheral blood biomarker that is easy to detect, Tfh cells have high clinical application value.[23] By measuring the number or functional status of Tfh cells in a patient's peripheral blood, physicians can initially assess the potential for patients to respond to ICIs and thus develop more personalized treatment regimens.[24]

From a statistical standpoint, the AUC of 0.902 is remarkably high, indicating the exceptional performance of Tfh cells as a predictor, effectively discriminating between patients with favorable and poor responses to ICI treatment. This high prediction accuracy not only reflects the core position of Tfh cells in tumor immune response, but also provides us with confidence to explore more immune cell-based prognostic markers.[25] Moreover, the high sensitivity and specificity observed for Tfh cells further solidify their reliability as a predictor. The high sensitivity ensures accurate identification of patients who are likely to respond favorably to ICI treatment, minimizing the risk of missed diagnoses. Concurrently, the high specificity allows for the accurate exclusion of patients unlikely to benefit from ICI therapy, reducing the likelihood of misdiagnoses.[26] This remarkable combination of high sensitivity and specificity renders Tfh cells a valuable tool for predicting ICI treatment response, demonstrating exceptional stability.[27] The observed sensitivity of 100% and specificity of 80.70% for Tfh cells further emphasize their potential as a reliable biomarker.

From a biological perspective, the high predictive accuracy of Tfh cells is likely intertwined with their pivotal role in orchestrating humoral immune responses. As an important accessory cell for B cell differentiation and antibody production, Tfh cells directly participate in the process of anti-tumor immune response by promoting B cell activation, proliferation and antibody class switching.[28] Therefore, Tfh cell numbers and functional status can serve as direct indicators of the strength and efficacy of a patient's humoral immune response, providing valuable insights into their potential response to ICI therapy. Furthermore, the observed stability in Tfh cell-based prediction may stem from their central role in immune responses. As an important helper cell for B cell activation and antibody production, Tfh cells play an irreplaceable role in humoral immune responses.[29] Consequently, any fluctuations in their numbers or functional status directly reflect the status and efficacy of a patient's immune response, enabling stable and accurate prediction of their response to ICI treatment.[30]

This study makes a statistically significant contribution to the field by highlighting the intricate nature of the immune response and investigating the predictive value of peripheral blood Tfh cells in assessing the short-term prognosis of HCC patients receiving ICI therapy. Firstly, it provides a deeper understanding of the complexities inherent in tumor treatment responses. Monitoring Tfh cell numbers and function offers valuable insights into the activation status of the patient's immune system, the intricate interplay between immune cells, and potential immune escape mechanisms, ultimately contributing to a more comprehensive understanding of the tumor immune response. Secondly, it guides the development of personalized treatment strategies, a cornerstone of modern medicine. By evaluating the predictive value of peripheral blood Tfh cells, clinicians can tailor treatment plans for HCC patients with greater precision. Patients with robust Tfh cell numbers or functional status may be ideal candidates for ICI therapy, while those with impaired Tfh cell function or evidence of immune escape mechanisms may benefit from alternative treatment modalities or combination therapies to enhance treatment efficacy and improve survival outcomes.

Despite the promising findings, it is crucial to acknowledge the limitations of this study. Firstly, the retrospective design inherently carries the risk of selection bias. Secondly, the relatively short follow-up period hinders the assessment of the long-term prognostic value of Tfh cells. Future studies with larger sample sizes and extended follow-up durations are warranted to validate these findings and explore the association between Tfh cells and long-term outcomes. Moreover, this study focused solely on peripheral blood Tfh cells. Investigating the prognostic significance of Tfh cells within the tumor microenvironment could provide further insights into their role in HCC progression and response to ICIs. Lastly, potential confounders, such as the use of different ICI regimens and the presence of comorbidities, were not fully accounted for. Future studies should consider adjusting for these factors to strengthen the validity of the findings.

In conclusion, this study demonstrated that Tfh cells were an independent predictor of short-term prognosis in patients with HCC receiving ICIs, and high levels of Tfh cells predicted a better short-term prognosis. This finding provides an important reference for clinical decision-making and provides a new direction for future research on tumor immunotherapy and the prediction of efficacy of ICIs. However, due to the limitations of this study, more in-depth and comprehensive studies are needed in the future to further validate and expand the predictive value of Tfh cells.

STATEMENT OF ETHICS

All subjects were approved by the Ethics Committee of The First Affiliated Hospital of Fujian Medical University (No.2020-217).

FUNDING

This study was approved by Fujian Natural Science Foundation project (No.2020J05252).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The data are available from the corresponding author on reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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