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ORIGINAL RESEARCH

Early Recurrent Hepatocellular Carcinoma with CK19 Positive Receiving Transarterial Chemoembolization After Surgical Resection: A Novel Risk Model Study

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Objective: To evaluate the benefit of nomogram-based model for predicting response and survival in patients with early recurrent hepatocellular carcinoma after hepatic resection by CK19 positive expression treated with transarterial chemoembolization (TACE).

Materials and Methods: We retrospectively analyzed 82 patients with early recurrent HCC expressing CK19 positivity after hepatectomy who underwent TACE between January 2014 and December 2023. OS and PFS were compared using the Kaplan-Meier method and Log rank test. Based on the COX regression results, independent predictors were identified from them. These factors were used to construct a nomogram model. The discriminatory, predictive efficacy of this model was assessed using receiver operating characteristic curves (ROC), calibration curves, and internal validation.

Results: CK19 expression grade and distant metastasis were independent prognostic risk factors, and the number of TACE sessions and whether it was combined with systemic therapy were prognostic protective factors, and survival after resection was strongly correlated with the CK19 grade. Compared with TACE alone, TACE combined with targeted and immunotherapy provided more survival benefit for patients with CK19-positive postoperative recurrence. The nomogram model has promising predictive efficacy.

Conclusion: We constructed a validated tool for the prognosis of patients with postoperative recurrence of hepatocellular carcinoma, which helps to identify the risk level of hepatocellular carcinoma recurrence and optimize the treatment as early as possible in the clinic, and brings survival benefit to patients.

Keywords: hepatocellular carcinoma, early recurrence, CK19, transarterial chemoembolization, prognostic model

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the fourth leading cause of cancer-related deaths worldwide, which is a disease with considerable clinical heterogeneity, exhibiting a range of behaviors and outcomes.[1] One of the most significant subtypes of HCC is characterized by the expression of Cytokeratin 19 (CK19), a marker that is typically associated with biliary epithelial cells and progenitor cells.[2] The presence of CK19 has been linked to more aggressive tumor behavior, poorer overall survival and an increased risk of early tumor recurrence following hepatectomy and liver transplantation.[3]

The presence of CK19 in HCC is believed to indicate a subset of the disease that may originate from liver progenitor cells and is influenced by extracellular stimuli such as hypoxia. It has been demonstrated that CK19-positive HCC cells display stem-like characteristics and are associated with resistance to chemotherapy and local treatments.[4–6] The regulatory network associated with CK19 expression involves a number of signaling pathways and transcription factors,

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including TGF-β, MAPK/JNK, MEK-ERK1/2, as well as noncoding RNAs, which contribute to the malignant properties of HCC.[7–11]

In the context of treatment, transarterial chemoembolization (TACE) is a widely utilized method for managing HCC.[12] However, CK19-positive HCC may respond differently and more refractory to TACE than CK19-negative tumors in our pervious research.[13] Moreover, some studies have indicated that the presence of CK19 may be a potential predictor of resistance to TACE and other therapies, underscoring the necessity for personalized treatment strategies for this specific subtype of HCC.[7,14–16]

In light of the distinctive attributes of CK19-positive HCC, there is a mounting interest in devising innovative therapeutic modalities that are specifically designed to target this particular subtype. For instance, the targeting of the TGFβR1 pathway has emerged as a promising therapeutic avenue for CK19-positive HCC, given that TGF-β signaling has been linked to the regulation of CK19 expression and the aggressive behavior of these tumors.[17]

Our previous study on CK19-positive patients undergoing TACE treatment still has plenty of limitations,[13] the current study aimed to investigate the prognosis of early recurrence CK19-positive-HCC following TACE treatment. We also need to assess the safety of TACE in this cohort and endeavored to develop a well-examined prognostic model. We hope this study will offer actionable insights to inform clinical strategies for the treatment of early recurrent HCC characterized by CK19 positivity.

Materials and Methods

Study Design

The study was approved by the institutional review board of the First Affiliated Hospital of Nanjing Medical University and Jiangsu Province Hospital of Chinese Medicine. The clinical data of 82 patients who had received TACE treatment for early recurrent hepatocellular carcinoma after resection in the Department of Interventional Radiology of two institution during January 2014 to December 2023 were collected and collated, and the liver histopathology was evaluated by two liver histopathologists, and immunohistochemical staining was carried out in the post-operation period. They were divided into two groups based on CK19 expression. The data collected mainly included age, gender, hepatitis B virus (HBV) infection, maximum diameter of the tumor, number of tumors, blood count, biochemistry, coagulation, liver Child-Pugh classification, physical status, number of TACE sessions and whether or not the treatment was combined with systemic therapy. The inclusion criteria were: (1) CK19 expression was detected by immunohistochemistry; (2) early recurrence was diagnosed within 2 years after surgery; (3) at least one TACE treatment was received with a postoperative interval of at least 1 month; (4) the Child-Pugh score ranged from A5 to B7. Patient exclusion criteria were: (1) TACE was received as an adjuvant therapy within one month after surgery; (2) other types of hepatic malignant tumors were diagnosed, such as cholangiocellular carcinoma; (3) the number of TACE treatments was not enough for the patients to receive the treatment. Patients were excluded if they had received TACE as adjuvant therapy within one month after surgery; (1) were diagnosed with other types of liver malignancy, such as cholangiocellular carcinoma, neuroepithelial carcinoma, or metastatic carcinoma; (2) had incomplete medical information or had been lost to follow-up.

Immunohistochemical Detection

Liver tissue samples collected after surgery were fixed in a solution containing 10% neutral buffered formalin. The fixed samples were then dehydrated, washed and embedded in paraffin. The paraffin-embedded samples were cut into thin slices, each 4 µm thick. To remove the paraffin, the slices were deparaffinised in xylene and then rehydrated in a series of alcohol solutions of increasing concentrations. For antigen extraction, the sections were heat-treated in a microwave oven using citrate buffer with a pH of 6.0. The heat treatment temperature was 100°C for 2–3 minutes. Subsequently, the sections were treated with 3% hydrogen peroxide for 15 min to block endogenous peroxidase activity. Then, the sections were incubated with mouse anti-CK19 antibody diluted at 1:200 with antibody diluent provided by Maxin (Fuzhou, China). The incubation temperature was 37°C for 1 hour. After incubation, the sections are rinsed with PBS (phosphate buffered saline) and then incubated with horseradish peroxidase-labelled rabbit or mouse immunoglobulin, also provided by Maxim. The immunoglobulin solution is incubated at 25°C for 20 minutes. After rinsing again with PBS, the sections were incubated with diaminobenzidine (DAB) for 10 minutes to visualise the staining. Finally, the sections were counterstained with hematoxylin. To ensure the reliability of the staining results, CK19-positive tissue sections provided by Maxin Immunostaining Kit (Kit-5020, Fuzhou, China) were added as positive controls in the analysis. Negative control used PBS instead of primary antibody. Both positive and negative controls were analyzed together with patient samples. To determine the percentage of cells staining positive for CK19, two senior pathologists independently examined the microscopic field of view. The results of the examination were classified into three categories, *CK19 (local/focal positivity)* was recorded as grade I positivity, result *CK19 (+)* was recorded as grade II positivity, result *CK19 (++)* was recorded as grade III positivity.

TACE Procedure

Routine preparation of TACE procedure, after local infiltration anesthesia, first through the femoral artery puncture, through the femoral artery puncture point into the 5F catheter sheath, delivery of 5F RH catheter, and routinely selective access to the superior mesenteric artery and the celiac trunk for imaging. After a definitive diagnosis of the tumors' feeder artery, a microcatheter was used as needed to superselectively access the tumor's feeder artery, which was later confirmed by angiography. Then, according to the preoperative assessment of liver function grade and intraoperative imaging, raltitrexed and lopressor were injected into the hepatic innominate artery (the dose was calculated according to the body surface area), and then appropriate amount of iodinated oil mixed with chemotherapeutic agents was injected for embolization, and then according to the degree of embolization by imaging, the gelatin sponge was assisted in reinforcing embolism until the blood supply of the tumor was basically blocked by the imaging.

Follow-Up and Evaluation

All patients were closely followed until death or the end of the study (31 December 2023). To record TACE-related adverse events (TrAEs), blood tests, including complete blood counts, liver, renal and cardiac biomarkers, and thyroid function, were performed at 1 week and 1 month after TACE procedures. When residual surviving tumor was detected or new lesions appeared, after discussion with the multidisciplinary team, and based on tumor status, liver function and general patient.

Results

Patient Data

From January 2014 to December 2023, clinical data were collected from 82 patients with recurrent HCC who underwent TACE treatment for CK19-positive status following surgical resection at two centers. A detailed flowchart of the study is presented in Figure 1. The majority of these patients had hepatitis B-related HCC (71 out of 82), with pathological results indicating CK19 positivity at grade I in 34 cases, grade II in 37 cases, and grade III in 11 cases. A total of 47 patients received TACE alone, 10 received TACE combined with Tyrosine kinase inhibitors (TKIs), 5 received TACE combined with immune checkpoint inhibitors (ICIs), and 20 received TACE combined with both TKIs and ICIs. The median follow-up duration was 305 days, and the median time to recurrence was 194 days. Detailed baseline characteristics are presented in Table 1.

OS&PFS Regression Analysis and Forest Plot

Univariate Cox proportional hazards model analysis (Table 2) revealed significant associations between Barcelona Clinic Liver Cancer (BCLC) staging, treatment modality, CK19 expression grading, presence of metastasis, and the number of TACE sessions with OS. Based on a threshold of P-value less than 0.2, these significant factors were further included in the multivariate Cox regression analysis. The final analysis indicated that BCLC staging, combined treatment modality, CK19 expression grading, metastatic status, and the number of TACE sessions were all independent prognostic factors for OS. Notably, among these factors, the treatment modality involving systemic therapy and the number of TACE sessions were identified as protective prognostic factors for OS, whereas metastasis and high CK19 grading were

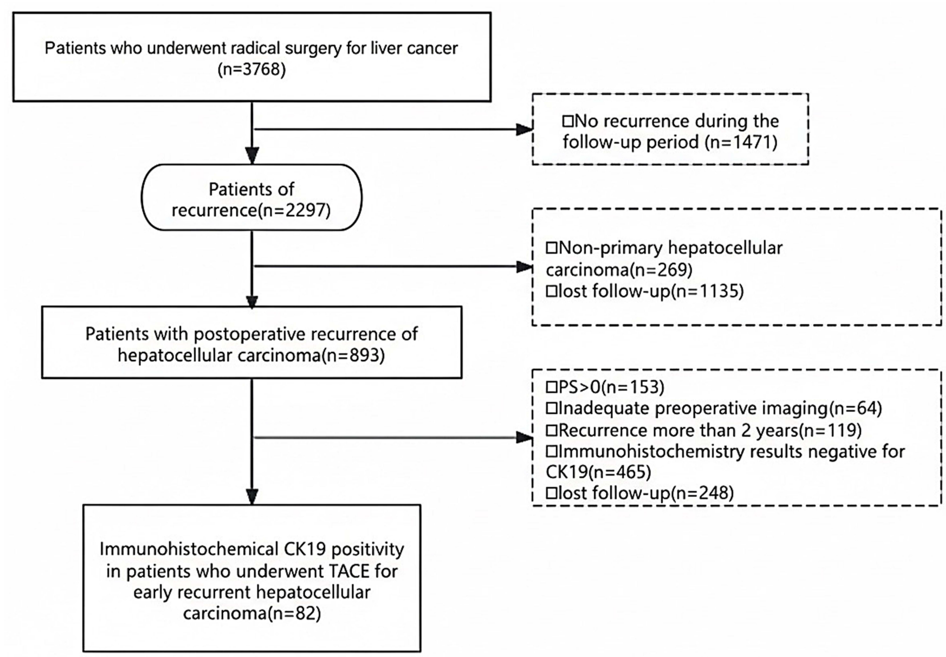

Figure 1 Flow chart of enrollment.

considered as risk prognostic factors for OS. Based on the results of the Cox regression analysis, we constructed a forest plot (Figure 2) to visually display the impact and statistical significance of each prognostic factor on OS.

Subgroup and Kaplan-Meier Survival Analysis

Patients were stratified based on the expression grading of CK19, and the survival times of different groups were compared. The results showed a significant correlation between CK19 expression grade and OS ($p<0.001$): the median survival time for patients with CK19 grade I was 1500 days, for grade II it was 518 days, and for grade III it was 312 days. Additionally, PFS also significantly decreased with the increase in CK19 expression grade: the median PFS for patients with CK19 grade I was 275 days, for grade II it was 145 days, and for grade III it was 49 days (Figure 3A and B). Furthermore, we classified

Table 1 Baseline Characteristics

Characteristic		**n=82**
Sex		
	Male	72
	Female	10
Age (years)		58.41±1.154
Immunophenotype		
	HCC	67
	DPHCC	15
CK19 expression		
	Local/focal positivity	34
	Secondary positivity	37
	Tertiary positivity	11
ECOG		
	0	76
	1	6

(*Continued*)

Table 1 (Continued).

Characteristic		n=82
BCLC stage		
	A	56
	B	14
	C	12
Child-Pugh grade		
	A	74
	B	8
ALBI grade		
	1	28
	2	49
	3	5
Tumor size		
	<5 cm	50
	≥5 cm	32
Tumor number		
	<3	44
	≥3	38
Macrovascular invasion		
	Yes	28
	No	54
Metastasis		
	Yes	42
	No	40
AFP (ng/mL)		
	<20	37
	≥20 and <200	15
	≧200	30
No. of TACE sessions		2.72±0.242
Treatment		
	TACE	47
	TACE+TKI	10
	TACE+ICI	5
	TACE+TKI+ICI	20
Recurrence time		194.73±23.573

Abbreviations: ALBI, albumin-bilirubin; AFP, alpha-fetoprotein; TACE, trans-arterial chemoembolization; DPHCC, dual-phenotype hepatocellular carcinoma; TKIs, tyrosine kinase inhibitors; ICIs, immune-checkpoint Inhibitors.

and compared patients based on the specific treatment modalities they received (TACE alone, TACE combined with TKIs, TACE combined with ICIs, and TACE combined with both TKIs and ICIs). The analysis revealed no statistically significant differences in OS and PFS among these different treatment modalities (p>0.05). However, when comparing patients who received TACE alone with those who received TACE combined with any other treatment modality, there was a significant difference in overall survival time (TACE alone was 486 days, while TACE combined with systematic treatment was 801 days, p=0.015). In particular, when comparing patients who received TACE alone with those who received TACE combined with both targeted and immunotherapy, there was also a significant difference in overall survival time (TACE alone was 486 days, TACE combined with TKIs and ICIs was 762 days, p=0.044) (Figure 4A–C). Nevertheless, the comparison of Progression-Free Survival (PFS) between these treatment modalities did not reach statistical significance (p>0.05).

Table 2 COX Regression Analysis of OS

Characteristic	Univariate Analysis		Multivariate Analysis	
	95% CI	p-value	95% CI	p-value
Age (years)	0.993–1.073	0.111		
Sex	0.141–1.583	0.224		
ECOG	0.378–7.088	0.510		
Child-Pugh grade (A vs B)	0.558–8.256	0.266		
ALBI grade (1 vs 2 vs 3)	0.616–3.412	0.395		
BCLC grade	0.065–1.281	0.076		
Edmondson grade	0.534–2.154	0.845		
CK19 classification	2.050–7.304	0.001	2.020–4.920	0.001
Tumor size (<5 cm vs ≥5 cm)	0.580–2.542	0.607		
Tumor number (<2 vs ≥2)	0.250–1.556	0.311		
Macrovascular invasion	0.520–3.000	0.620		
Microvascular invasion	0.586–2.544	0.594		
Metastasis	1.428–6.929	0.004	1.303–4.584	0.005
AFP (<20 UI/mL vs ≤20 and <200 UI/mL vs ≥200 UI/mL)	0.865–2.337	0.165		
Treatment (TACE+TKI+ICI vs TACE+ICI vs TACE+TKI vs TACE)	0.548–0.843	0.001	0.609–0.896	0.002
No. of TACE sessions	0.644–0.973	0.26	0.661–0.928	0.005

Abbreiations: AFP, alpha-fetoprotein; TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; ICIs, immune-checkpoint Inhibitors.

Construction of Nomogram and Internal Validation

In this study, a nomogram was meticulously constructed to predict the survival of patients with postoperative recurrence of liver cancer by selecting the four most predictive variables (Figure 5). The model demonstrated good discrimination with an Area Under the Curve (AUC) of 0.859 and 0.916 at one and two years, respectively. The Concordance Index (C-index) of the model was 0.794, with a 95% Confidence Interval (CI) ranging from 0.732 to 0.855, further confirming the robustness of the model. Among the variables included in the model, the regression coefficient for the number of TACE treatments was −0.206, with a Hazard Ratio of 0.814, indicating that each additional TACE treatment reduced the risk of positive events by 18.6%, which is statistically significant (p=0.016), with a 95% CI of 0.688 to 0.962. The regression coefficient for CK19 expression was 1.14, with an HR of 3.127, meaning that the risk of positive events for

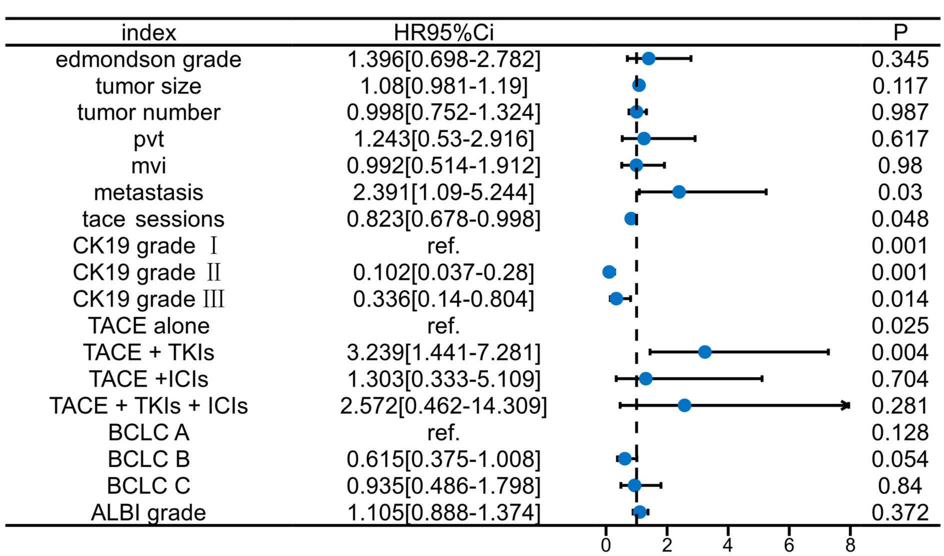

Figure 2 Forest plot.

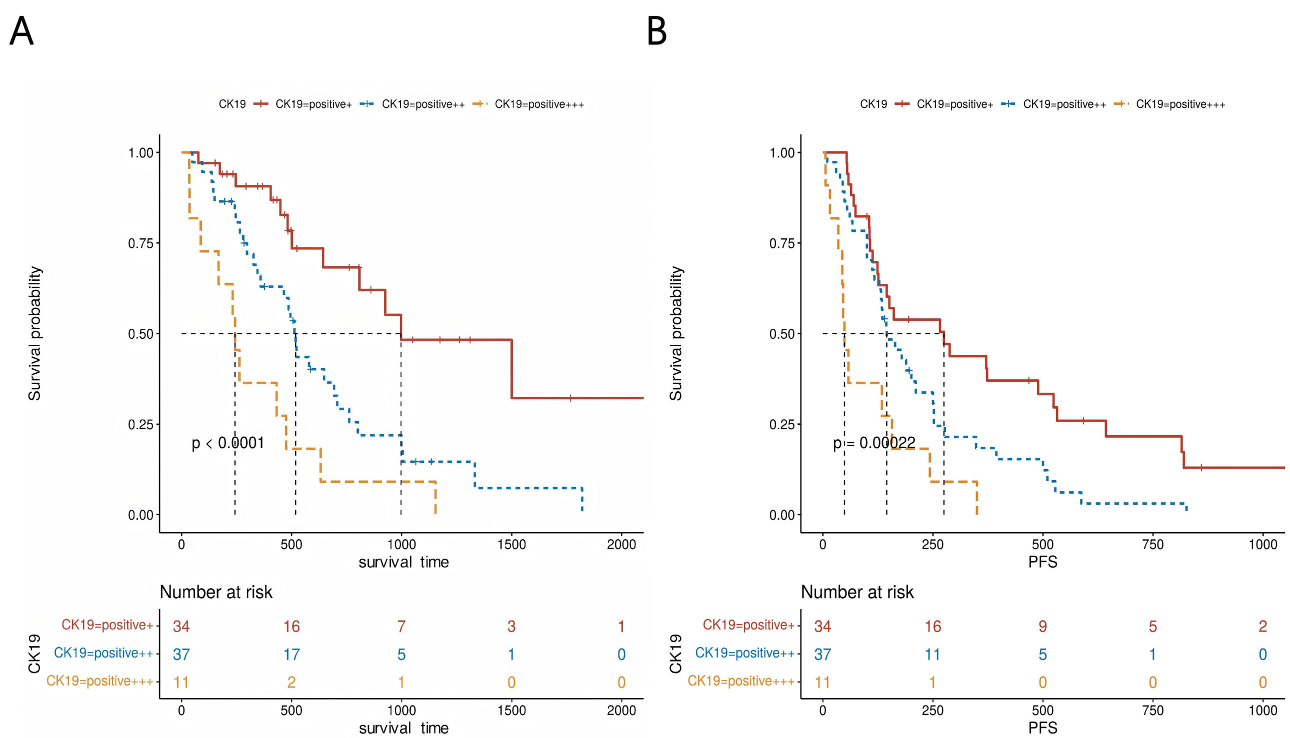

Figure 3 Kaplan-Meier curves by CK19 expression classification (**A**) Overall survival (**B**) Progression-free survival.

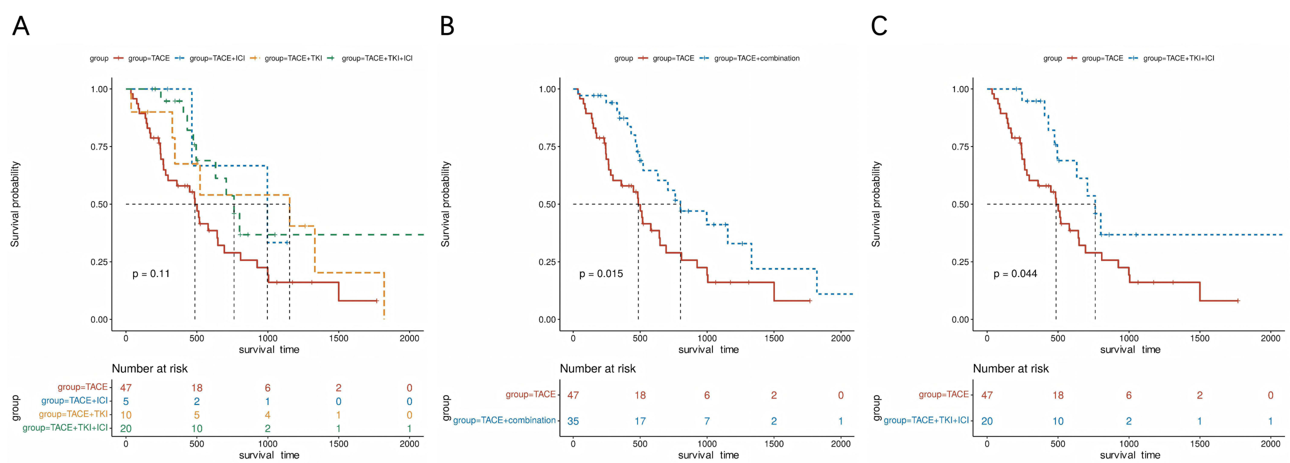

Figure 4 Kaplan-Meier curves grouped by different treatment modalities (**A**) Comparison of overall survival between TACE only and TACE+TKI, TACE+ICI, TACE+TKI +ICI; (**B**) Comparison of overall survival between TACE only and TACE combined with any treatment; (**C**) Comparison of overall survival between TACE only and TACE combined with targeted immunotherapy.

patients with positive CK19 expression significantly increased by 212.7% (p<0.05), with a 95% CI of 2.003 to 4.882. Additionally, the regression coefficient for metastasis occurrence was 0.854, with an HR of 2.349, indicating that the risk of metastasis occurrence increased by 134.9% (p=0.007), with a 95% CI of 1.262 to 4.372. The regression coefficient for the treatment modality was −1.087, with an HR of 0.337, suggesting that a change in treatment modality reduced the risk of positive events by 66.3% (p=0.001), with a 95% CI of 0.174 to 0.653. Calibration curve analysis (Figure 6) shows a high degree of consistency between the calibrated curve and the ideal curve, indicating a good fit between the model's predicted survival rates and the actual observed outcomes. Furthermore, the AUC showed good stability at different time points (Figure 7), further validating the predictive accuracy of the model.

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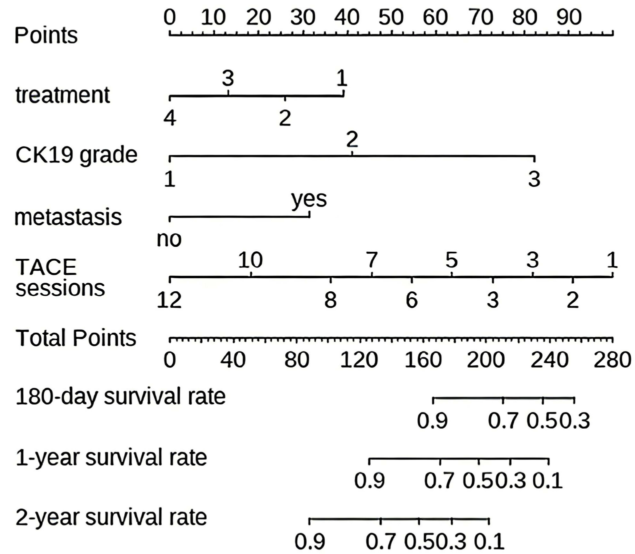

Figure 5 Nomogram model based on COX regression. Treatment 1: TACE-only group; Treatment 2: TACE+TKIs group; Treatment 3: TACE+ICIs group; Treatment 4: TACE+TKIs+ICIs group.

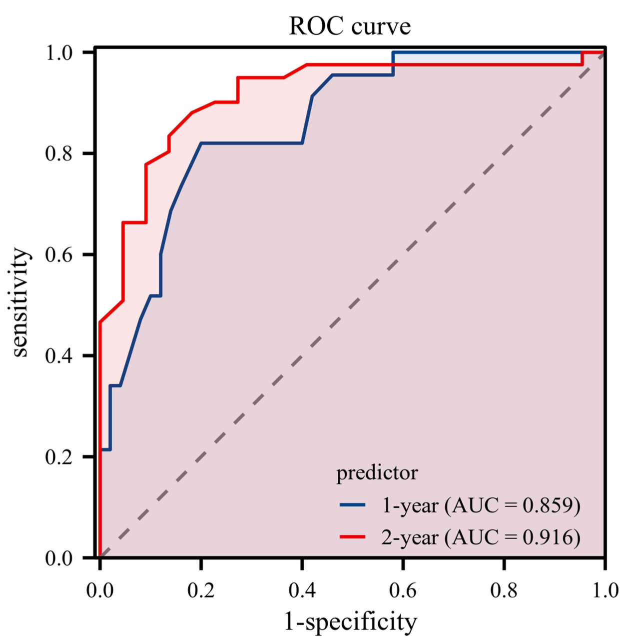

Figure 6 Area under curve compared between 1-year and 2-year.

Disscusion

The aim of this study was to conduct an in-depth analysis of the prognostic differences among patients with positive CK19 expression in the recurrence of HCC after surgical resection, when treated with TACE combined with different therapeutic regimens. The findings indicate that CK19 expression grading and the presence of distant metastasis are two independent prognostic risk factors. Concurrently, the number of TACE treatments and the combination with systemic therapy are recognized as protective prognostic factors. The predictive model constructed in this study has demonstrated exceptional predictive efficacy, providing robust decision support for personalized treatment of patients with post-operative recurrence of HCC.

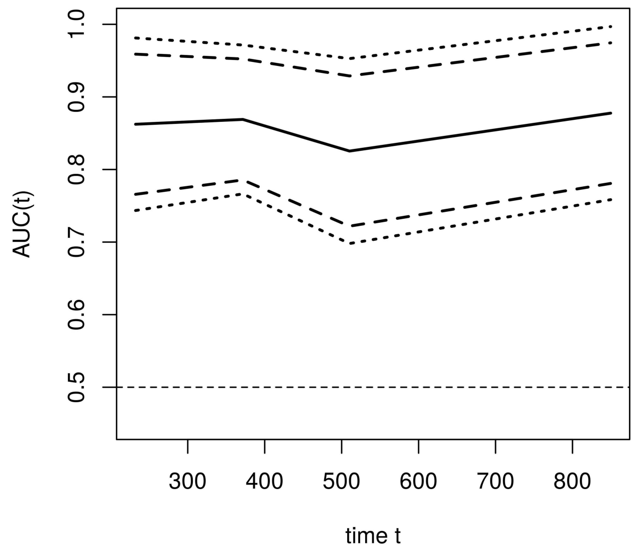

Figure 7 Area under the curve with time-dependent ROC.

CK19 is a specific marker for biliary epithelial cells and hepatic progenitor cells in the adult liver, and its expression in some HCCs has been confirmed as a predictor of poor prognosis. The recently proposed classification of primary liver cancer histopathology categorizes CK19-positive HCC as a type of HCC with a stem cell/progenitor cell immune phenotype, while dual phenotype hepatocellular carcinoma (DPHCC) is defined as a classic type of combined hepatocholangiocarcinoma.[3] According to this novel classification framework, CK19+ HCC and DPHCC form a continuous spectrum between HCC and cholangiocarcinoma, with CK19+ HCC being biologically closer to HCC and DPHCC tending more towards CC.[17] The increase in biliary phenotype components in primary liver cancer may lead to poor prognosis after surgical treatment.

In this study, strong positive expression of CK19, similar to DPHCC, was associated with high recurrence rates and poor response to various treatment strategies. Moreover, CK19 and CK7 have been proven to be related to the potential metastatic capacity of tumor cells.[18,19] The study also points out that there is a significant association between post-operative distant metastasis of liver cancer and poor patient prognosis. Other studies have shown that CK19 positivity has a synergistic effect with microvascular invasion, and residual tumor cells may accelerate the process of distant metastasis.[20] The heterogeneity of liver cancer is extremely complex, involving multiple signaling pathways, such as extracellular matrix (ECM) receptor interactions, transforming growth factor-β (TGF-β) signaling pathways, Notch signaling pathways, phosphatidylinositol 3-kinase-Akt (PI3K-Akt) signaling pathways, Wnt signaling pathways, and tumor necrosis factor (TNF) signaling pathways. Enrichment analysis of these pathways indicates that the high expression of CK19 may be closely related to key biological processes such as tumor invasion, proliferation, immune evasion, and cell fate determination.[21] In this study, patients with different levels of CK19 expression showed significant differences in survival prognosis, with higher levels of CK19 expression tending to exhibit characteristics of cholangiocarcinoma.

Recent studies suggest that TACE may have a positive impact on the OS of CK19-positive HCC patients, a finding consistent with previous research results. As a common adjuvant therapy for liver cancer after surgery, TACE has been proven to significantly extend the PFS of patients with high recurrence risk and CK19-positive HCC, although its effect on extending OS has not yet been confirmed.[22] In addition, a meta-analysis further supports the potential benefits of TACE in improving the OS and PFS of patients with MVI after surgery.[23] Tumor hypoxia induced by TACE treatment may promote the release of vascular endothelial growth factor (VEGF), a mechanism that has been detailed in previous studies and will not be reiterated here. It is worth noting that a low expression level of CK19 is positively correlated with the survival benefit after adjuvant TACE treatment, while a high expression level may offset the survival benefits of

TACE. This phenomenon may reveal the role of CK19 in key biological processes such as tumor proliferation, angiogenesis, invasiveness, metastasis, and drug resistance.

Currently, it remains controversy in the research on the signaling pathways and potential targets of CK19-positive HCC. A study in Japan revealed that the TGF-β/Smad signaling pathway is activated in CK19-positive HCC cells. Accordingly, inhibitors of TGFβ receptor 1 (such as LY2157299) have been proven to effectively inhibit the proliferation of CK19-positive HCC cells. Based on these findings, TGFβR1 inhibitors are considered a promising new targeted treatment strategy for CK19-positive HCC.[11] A study conducted in China included 280 HCC patients who underwent surgical resection, some of whom received sorafenib treatment after surgery. The study showed no significant difference in OS between the two groups. However, in the CK19 and OV6 double-positive subgroup, patients who received sorafenib treatment showed better OS than those who did not receive treatment.[24] This indicates that CK19-positive HCC patients may benefit from postoperative sorafenib treatment. Govaere et al's study further confirmed the regulatory mechanism of CK19 through the PDGFRα-LAMB1-CK19 axis.[8] Therefore, inhibitors of PDGFRα, such as imatinib,[25] regorafenib,[26] cabozantinib[27] and lenvatinib,[28] may have specific efficacy for CK19-positive HCC. Nevertheless, the clinical application of these drugs still needs more clinical trials to verify their safety and efficacy.

The tumor immune microenvironment plays an extremely important role in the prognosis of liver cancer. A study by Gao et al revealed that the proportion of immunoexhausted cells such as regulatory T cells (Tregs) and programmed death ligand 1 positive (PD-L1+) CD4+ T cells in CK19-positive HCC patients was significantly higher than in CK19-negative patients.[29] This finding further suggests that CK19-positive HCC patients may have an immunosuppressive microenvironment, which may be the key to regulating the poor prognosis of CK19-positive HCC patients. This provides potential targets for the development of immunosuppressants. The current research proposes possible mechanisms including: (1) promoting the proliferation of regulatory T cells and myeloid-derived suppressor cells (MDSCs), and releasing more immunosuppressive cytokines;[30] (2) hindering the infiltration of T cells into tumor tissues;[31] (3) inhibiting the activation and maturation of dendritic cells (DCs), reducing the proliferation and activation of T cells.[32] In this study, a patient who received TACE combined with atezolizumab and bevacizumab showed a good prognosis.

This study has certain limitations. Firstly, it is a patient-insufficient retrospective study, and selection bias cannot be completely avoided, and the number of patient medical records is insufficient. Secondly, the prognostic model of this study has not been validated, nor has it included imaging parameters for prediction. Subsequently, the nomogram model has not been externally validated, and its predictive efficacy remains to be tested.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by Dr Zhu Di, without undue reservation.

Ethics Statement

This study is a retrospective research project which reviewed and approved by the Institutional Review Boards of The First Affiliated Hospital of Nanjing Medical University and Jiangsu Province Hospital of Chinese Medicine. Due to its retrospective nature and the anonymization of data, informed consent was waived by ethics committee. All procedures adhere to the ethical principles outlined in the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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