



## ORIGINAL ARTICLE

# Association of CK19 expression with the efficacy of adjuvant transarterial chemoembolization after hepatic resection in hepatocellular carcinoma patients at high risk of recurrence

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## ABSTRACT

**Background and Aim:** This study retrospectively explored the potential association between CK19 expression and efficacy of adjuvant conventional transarterial chemoembolization (TACE) after hepatic resection in patients with hepatocellular carcinoma (HCC) at high risk of recurrence.

**Methods:** Patients ( $n = 508$ ) who underwent hepatic resection between January 2012 and December 2017 were enrolled. Overall survival (OS) and recurrence-free survival (RFS) were compared between groups. Survival analysis was performed using the Kaplan-Meier method, and groups were compared using the log-rank test.

**Results:** OS and RFS were worse for CK19-positive patients than for CK19-negative patients, regardless of whether patients were matched on the basis of propensity scores. Among CK19-positive patients in the absence of propensity score matching, TACE was associated with better RFS. Among CK19-negative patients in the absence of propensity matching, TACE was associated with better OS and RFS. Among patients treated with TACE, CK19-positive patients showed worse OS but similar RFS as CK19-negative patients. Multivariate analysis identified the following independent predictors of worse OS: CK19 positivity, no adjuvant TACE, macrovascular invasion, microvascular invasion, tumor size  $>5$  cm, alanine transaminase  $>80$  U/L, and aspartate transaminase  $>80$  U/L. Multivariate analysis identified the following predictors of worse RFS: CK19 positivity, no adjuvant TACE, age  $\geq 60$  years, alpha-fetoprotein  $\geq 400$  ng/ml, and Barcelona Clinic Liver Cancer stage B/C.

**Conclusion:** This study suggests that among HCC patients at high risk of recurrence, adjuvant TACE can significantly prolong OS and RFS of CK19-negative patients, while it may prolong only RFS of CK19-positive patients.

**Relevance for Patients:** Not all patients will benefit from adjuvant TACE, therefore, it is necessary to select the best benefit subsets before TACE. By studying the relationship between CK19 expression and TACE benefit, it will be possible to help guide decision-making about adjuvant TACE in HCC patients at high risk of recurrence.

## 1. Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent malignant tumors in the world, and its incidence continues to rise [1]. Treatments for HCC include hepatic resection, liver transplantation, transarterial chemoembolization (TACE), radiation therapy, local ablation, and drug therapy. Long-term survival after hepatic resection is limited primarily by

postoperative HCC recurrence or metastasis, the rates of which at 5 years can be as high as 40-70% or even higher [2-4]. Therefore, it is important to reduce the rate of HCC recurrence. Risk factors for recurrence after hepatic resection include the combination of macrovascular invasion and microvascular invasion (MVI), multiple tumors, and tumor diameter  $\geq 5$  cm [5,6].

TACE is one of the standard therapy for patients with intermediate or advanced-stage HCC [7,8]. The principle of TACE is to promote tumor necrosis while preserving enough liver function to improve the patient's survival time. Local drug concentrations in TACE therapy were more than 10 times higher than in systemic therapy [9]. Several randomized controlled trials, retrospective studies, and meta-analyses revealed that postoperative adjuvant TACE could reduce recurrence risk for HCC patients at high risk of recurrence after hepatic resection [10-15]. Moreover, HCC official guideline in China also recommends adjuvant TACE for HCC patients at high risk of recurrence [16]. However, some investigators suggest that adjuvant TACE may suppress the patient's immune function and aggravate liver damage, thereby increasing the risk of recurrence [17]. In addition, patients can show resistance to the chemotherapy drugs in TACE [18,19]. It would be helpful to develop biomarkers that may help identify patients at high recurrent risk who are more likely to benefit from adjuvant TACE.

One such biomarker might be the cytokeratin CK19, a component of intermediate filaments in epithelial cells that are not normally expressed in normal liver cells but is expressed in HCC [20], where it serves as an independent risk factor for poor prognosis. While CK19 expression is difficult to assess preoperatively [21,22], it can be analyzed after surgery by histopathology, leading us to ask whether it might be a useful prognostic predictor in patients undergoing curative resection in the presence or absence of adjuvant TACE.

Therefore, the present retrospective study analyzed whether CK19 expression is associated with overall survival (OS) and recurrence-free survival (RFS) of HCC patients undergoing hepatic resection who are at high risk of recurrence. Survival between patients negative or positive for CK19 and who underwent adjuvant TACE or not were compared.

## 2. Methods

### 2.1. Patient

Patients were retrospectively enrolled if they underwent hepatic resection between January 1, 2012, and December 31, 2017, and if they showed one or more of the following risk factors for postoperative recurrence [16]: (1) Single tumor with MVI; (2)  $\geq 2$  tumors, with or without MVI; (3) tumor diameter  $\geq 5$  cm; or (4) large blood vessel invasion, defined as main or branched tumor thrombus in the portal vein, or hepatic vein tumor thrombus. Patients were enrolled only if (1) the hepatic resection was their initial treatment, and it involved complete tumor removal (negative margins), with no recurrence within the subsequent 30 days; (2) the patient's diagnosis of HCC was confirmed by pathology analysis of surgical samples; and (3) the patient's surgical samples were examined for CK19 expression using immunohistochemistry.

Patients were excluded from the study if they (1) had any other malignancy as well as HCC before hepatic resection; (2) had received any other treatments for HCC before hepatic resection, such as TACE or radiofrequency ablation; or (3) residual lesions were found during adjuvant TACE. Patients were also excluded if their clinical data were incomplete. This was a retrospective study that was conducted under the principles of the Declaration of Helsinki of 1975, therefore written informed consent was not provided by the patients. Ethics approval was obtained from the Ethical Review Committee of the center (LW2021060).

### 2.2. CK19 detection

CK19 was detected in biopsies using immunohistochemistry as described [23] and expression level was semi-quantified based on staining intensity (0 points, no stain; 1 point, light yellow; 2 points, brownish; 3 points, tan) and based on the percentage of positive cells (0 points,  $< 5\%$  of examined cells were positive; 1 point, 5-25%; 2 points, 26-50%; 3 points, 51-75%; 4 points,  $>75\%$ ). The two scores were multiplied together and resulting overall scores of 0-4 were classified as "CK19-negative" and scores of 5-12 as "CK19-positive."

### 2.3. TACE

The indication of adjuvant TACE was for patients with HCC at high risk of recurrence. These high-risk factors included preoperative macrovascular invasion, multinodular tumors, tumor diameter  $\geq 5$  cm, and postoperative MVI [6-9]. All patients with high-risk factors for recurrence routinely received adjuvant conventional TACE once within 4-6 weeks after hepatectomy, except those who refused to undergo the procedure, who were assigned to the non-TACE group. In the present institute, doctors strongly recommend adjuvant TACE in patients with multiple risk factors and may weakly recommend in others. Adjuvant TACE was performed as described [12]. An emulsion of pirarubicin or pharmorubicin (10-50 mg), oxaliplatin (25-100 mg), and lipiodol (2-10 mL) was infused into the hepatic artery of the operative side. Dosage is determined according to the height and weight of the patient. Adjuvant TACE outcomes were evaluated at 1-month follow-up by enhanced computed tomography (CT).

### 2.4. Outcomes

The primary outcome was OS, defined from the date of hepatic resection to the date of death or the date of the last follow-up. The secondary endpoint was RFS, calculated from the date of hepatic resection to the date of tumor recurrence or death, whichever occurred first. HCC recurrence was diagnosed using enhanced CT and/or magnetic resonance imaging (MRI) with or without alpha-fetoprotein (AFP)  $\geq 400$  ng/mL. Patients with HCC recurrence would be received appropriate therapeutic approaches, including radiofrequency ablation, repeat hepatic resection, TACE, or sorafenib. Patients with chronic hepatitis B routinely received antiviral therapy with nucleos(t)ide analogue [24,25].

All patients, whether they received adjuvant TACE or not, were followed up every 1-3 months during the first 2 years after

resection, then every 3-6 months thereafter. During follow-up visits, routine blood tests, tests of liver and kidney function, and assay of AFP were performed. In addition, liver B ultrasonography, CT and/or MRI with dynamic enhancement were performed. If AFP remained stable and imaging did not identify new lesions, then patients continued with routine follow-up.

If, however, CT and/or MRI with dynamic enhancement showed liver neoplasm, then the patient was diagnosed with recurrence and he or she was treated based on his or her medical condition, physical condition, tumor location, and residual liver function. Patients in adequate condition with sufficient residual liver function usually underwent repeat resection or ablation; otherwise, TACE or other palliative comprehensive treatment was considered [2]. All subjects were followed up until death or October 31, 2019.

### 2.5. Statistical analysis

Clinical data were expressed as frequencies and percentages. Continuous variables were abnormal distribution and were therefore reported as median (interquartile range). Categorical variables were compared with the  $\chi^2$  or Fisher's exact test, and continuous variables with the Mann-Whitney U test. Statistical analyses were performed using SPSS 22.0, and a two-tailed  $P < 0.05$  was considered statistically significant. Survival analysis was performed using the Kaplan-Meier method, and groups were compared using the log-rank test. Cox regression was used for univariate and multivariate analysis, and results were expressed as risk ratios with 95% confidence intervals.

In order to reduce the baseline bias between CK19-positive and negative groups, propensity score matching was performed in SPSS based on logistic regression that took into account the following factors: adjuvant TACE, sex, family history, age, cirrhosis, macrovascular invasion, MVI, tumor number, tumor size, hepatitis B surface antigen, platelet count, prothrombin time, albumin, alanine aminotransferase, aspartate aminotransferase, ascites, AFP, tumor envelope, total bilirubin, Child-Pugh classification, and Barcelona Clinic Liver Cancer (BCLC) stage. Propensity values were allowed to range from 0 to 1, and the 2:1 nearest neighbor matching method was used.

## 3. Results

From January 1, 2012, to December 31, 2017, 508 HCC patients with risk factors for postoperative recurrence were treated (Figure 1). This group comprised 436 men and 72 women aged 18-81 years (median age, 50 years). Just under half of patients (242) had single tumors and MVI, 336 had tumors of diameter  $\geq 5$  cm, 234 had at least two tumors, and 196 had macrovascular invasion. Of the 508 patients, 202 (40%) received adjuvant TACE treatment and 142 (28%) were CK19-positive. Of the 142 CK19-positive patients, 53 (37%) underwent adjuvant TACE. Of the 366 CK19-negative patients, 149 (41%) received adjuvant TACE (Table 1).

The CK19-positive group contained significantly higher proportions of patients with macrovascular invasion ( $P = 0.015$ ) and incomplete tumor envelope ( $P = 0.007$ ) than the CK19-negative group. In addition, CK19-positive patients showed

significantly higher AFP ( $P = 0.029$ ) and significantly lower alanine aminotransferase ( $P = 0.019$ ). After propensity score matching, the two groups of patients showed no significant differences in baseline characteristics (Table 1).

### 3.1. Association of CK19 expression with OS or RFS

Without propensity matching, OS was significantly shorter for the 142 CK19-positive patients than for the 366 CK19-negative patients ( $P = 0.001$ , Figure 2A); a similar result was observed for RFS ( $P = 0.011$ , Figure 2B). OS rates were 70% at 1 year, 46% at 3 years, and 43% at 4 years for CK19-positive patients, lower than the corresponding rates of 79%, 62%, and 59% for CK19-negative patients. Much lower was the corresponding RFS rates of 32%, 14%, and 10% for CK19-positive patients, and 48%, 17%, and 14% for CK19-negative patients.

Similar results were observed after propensity matching. OS was significantly shorter for the 139 CK19-positive patients than for the 249 CK19-negative patients ( $P = 0.003$ , Figure 2C). The CK19-positive group also showed significantly shorter RFS ( $P = 0.013$ , Figure 2D). OS rates were 70% at 1 year, 45% at 3 years, and 43% at 4 years for CK19-positive patients, lower than the corresponding rates of 77%, 63%, and 58% for CK19-negative patients. Much lower was the corresponding RFS rates of 30%, 14%, and 9% for CK19-positive patients, and 44%, 20%, and 17% for CK19-negative patients.

### 3.2. Association of adjuvant TACE with OS or RFS, regardless of CK19 expression

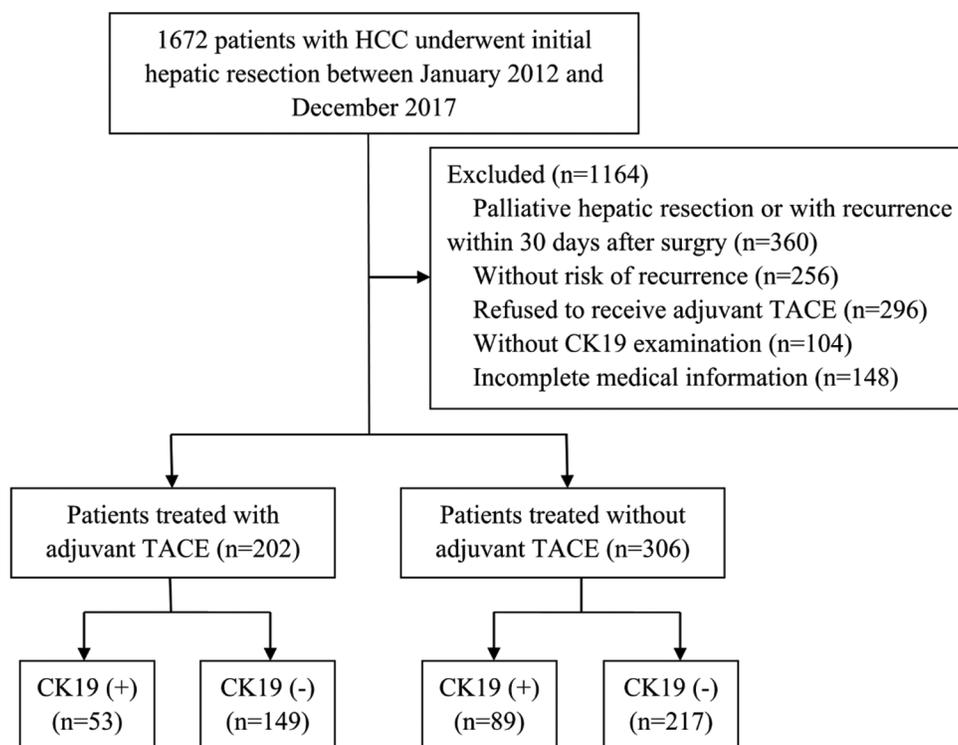
Before propensity matching, OS was significantly longer for the 202 patients who received adjuvant TACE than for the 306 patients who did not ( $P = 0.005$ , Figure 2E); a similar result was observed for RFS ( $P < 0.001$ , Figure 2F). After propensity matching, OS was significantly longer for the 231 patients who underwent adjuvant TACE than for the 157 patients who did not ( $P = 0.001$ , Figure 2G); a similar result was observed for RFS ( $P < 0.001$ , Figure 2H).

### 3.3. Association of adjuvant TACE with OS or RFS in CK19-positive patients

In the CK19-positive group, OS was not significantly different between the 53 patients who underwent adjuvant TACE or the 89 patients who did not ( $P = 0.193$ , Figure 3A). In contrast, RFS was significantly longer among those who underwent adjuvant TACE ( $P = 0.004$ , Figure 3B). In the CK19-negative group, OS and RFS were all significantly longer among the 217 CK19-negative patients who underwent adjuvant TACE than among the 149 who did not ( $P = 0.015$ , Figure 3C;  $P = 0.012$ , Figure 3D).

### 3.4. Uni- and multivariate analysis of factors associated with OS

Across all patients, single-factor analysis identified the following variables as significantly associated with worse OS (Table 2): CK19 positivity, no adjuvant TACE, macrovascular invasion, MVI, tumor diameter  $\geq 5$  cm, preoperative albumin  $\leq 35$  g/L, alanine aminotransferase  $> 80$  U/L, aspartate



**Figure 1.** Patient selection flow. HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization

**Table 1.** Baseline data of HCC patients with high-risk recurrent factors after hepatic resection.

Variables	Before propensity matching				After propensity matching			
	CK19 (-) (n=366)	CK19 (+) (n=142)	X/Z	P	CK19 (-) (n=249)	CK19 (+) (n=139)	X/Z	P
Male	315 (86.1)	121 (85.2)	0.061	0.887	220 (88.4)	118 (84.9)	0.952	0.346
HCC family history	60 (16.4)	23 (16.2)	0.003	1	36 (14.5)	23 (16.5)	0.302	0.659
Age (yrs.)	50 (44-57)	49 (41-59)	-1.513	0.130	50 (44-56)	49 (41-58)	-1.507	0.132
Liver cirrhosis	216 (59)	87 (61.3)	0.215	0.687	154 (61.8)	85 (61.2)	0.018	0.914
Macrovascular invasion	129 (35.2)	67 (47.2)	6.152	0.015	104 (41.8)	64 (46)	0.664	0.455
Microvascular invasion	273 (74.6)	94 (66.2)	3.594	0.061	173 (69.5)	94 (67.6)	0.143	0.732
Tumor number $\geq$ 2	160 (43.7)	74 (52.1)	2.903	0.093	107 (43)	72 (51.8)	2.797	0.111
Tumor size $>$ 5 cm	243 (66.4)	93 (65.5)	0.037	0.917	170 (68.3)	91 (65.5)	0.319	0.575
HBsAg (+)	317 (86.6)	113 (79.6)	3.895	0.055	212 (85.1)	110 (79.1)	2.278	0.159
Albumin (g/L)	40 (37-43)	40 (37-44)	-1.83	0.067	40 (37-43)	40 (37-44)	-1.382	0.167
Pre-albumin (mg/L)	183 (138-208)	183 (151-193)	-0.402	0.688	183 (142-209)	183 (150-197)	-0.112	0.911
Alanine transaminase (U/L)	37 (25-53)	32 (20-47)	-2.354	0.019	35 (24-49)	32 (20-46)	-1.384	0.166

aminotransferase  $>80$  U/L, AFP  $\geq 400$  ng/ml, and BCLC Stage B or C. Among these factors, multivariate analysis identified CK19 positivity, no adjuvant TACE, macrovascular invasion, MVI, tumor diameter  $\geq 5$  cm, alanine aminotransferase  $> 80$  U/L, and aspartate aminotransferase  $> 80$  U/L as independent risk factors of worse OS.

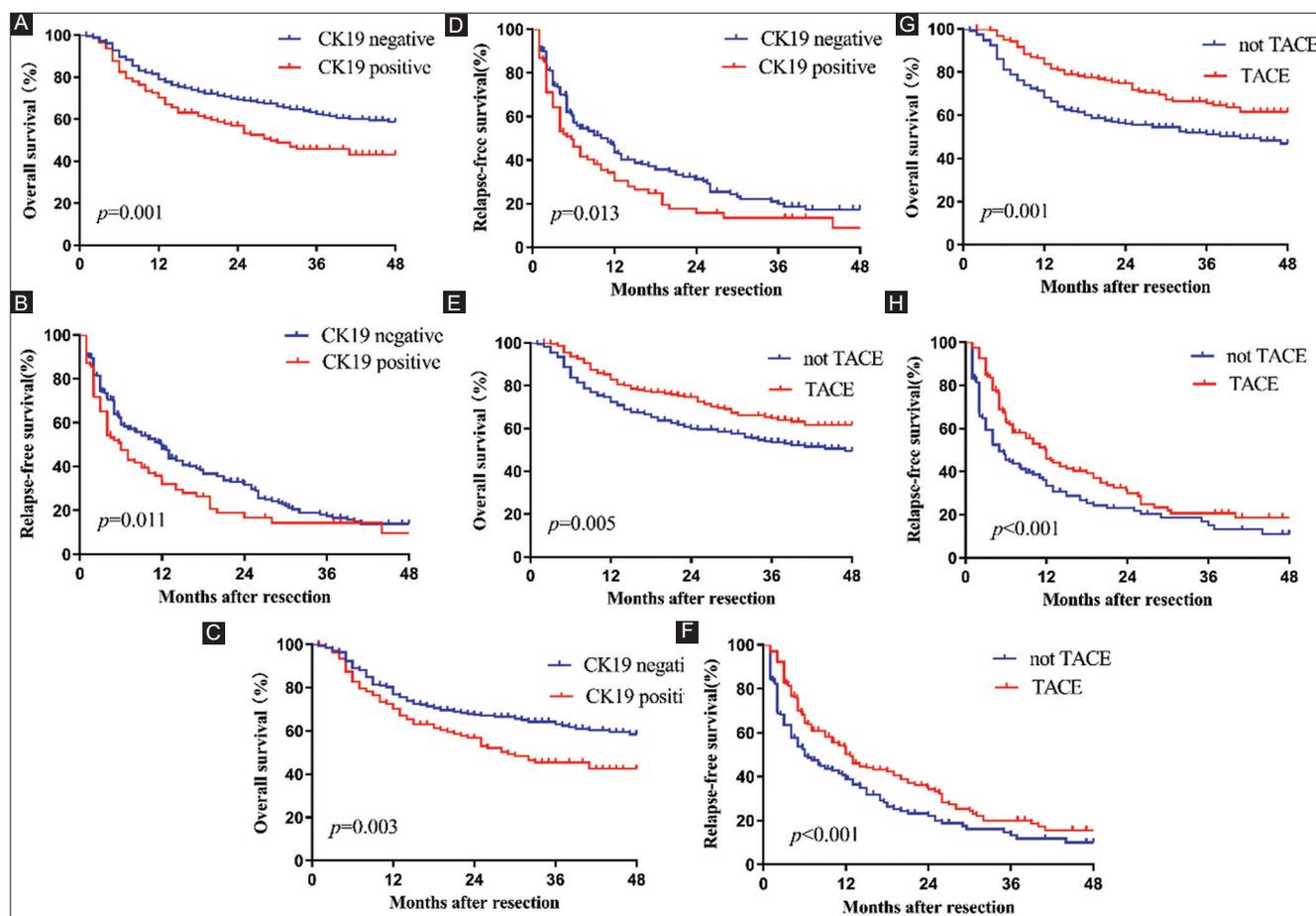
### 3.5. Uni- and multivariate analysis of factors associated with RFS

Univariate analysis identified the following factors as significantly associated with worse RFS: CK19 positivity,

no adjuvant TACE, age  $\geq 60$  years, macrovascular invasion, tumor diameter  $\geq 5$  cm, preoperative albumin  $\leq 35$  g/L, aspartate aminotransferase  $>80$  U/L, AFP  $\geq 400$  ng/ml and BCLC Stage C (Table 3). Among these, multivariate analysis identified CK19 positivity, no adjuvant TACE, age  $\geq 60$  years, AFP  $\geq 400$  ng/ml, and BCLC Stage B or C as independent risk factors for poor RFS.

## 4. Discussion

In this study, conducted in a region of exceptionally high HCC incidence in China and globally, we provide evidence that among HCC patients at high risk of recurrence, adjuvant TACE



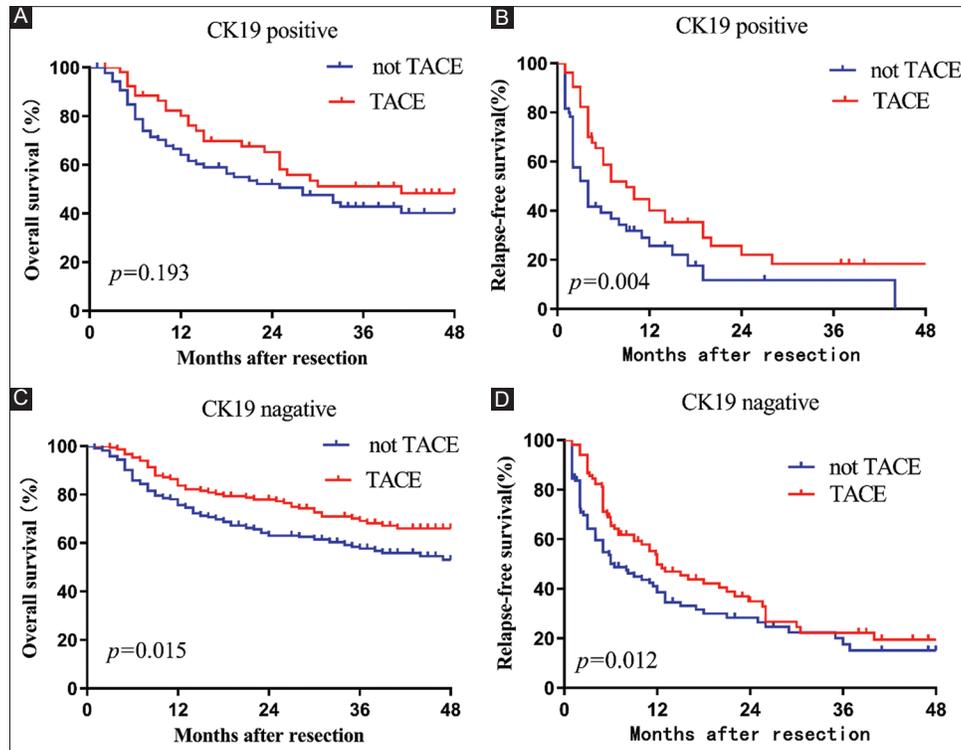
**Figure 2.** Kaplan-Meier survival curves for patients with hepatocellular carcinoma who underwent hepatic resection and were at high risk of recurrence. (A and B) Overall survival (OS) and recurrence-free survival (RFS) of patients before propensity score matching, stratified by CK19 status. (C and D) OS and RFS of patients after propensity score matching, stratified by CK19 status. (E and F) OS and RFS of patients before propensity score matching, stratified by transarterial chemoembolization (TACE). (G and H) OS and RFS of patients after propensity score matching, stratified by TACE

can significantly prolong OS and RFS if patients are CK19-negative. In contrast, it may prolong only RFS of CK19-positive patients.

Hepatic resection is performed on a substantial proportion of HCC patients, including those for whom resection is not formally recommended in the BCLC staging system [26-30]. While this has increased the number of HCC patients who can benefit from potentially curative therapy, rates of post-operative recurrence and metastasis remain high, sometimes above 50% [2,3]. Postoperative short-term recurrence (<2 years) is due mainly to intrahepatic metastasis, to which MVI contributes. Some studies have suggested that adjuvant TACE after hepatectomy can reduce recurrent rates in MVI-positive patients and increase OS and RFS rates in many patients, especially those with tumor diameter  $\geq 5$  cm and MVI [10-13,15,31]. On the other hand, the results suggest that adjuvant TACE may significantly prolong RFS but not OS of CK19-positive HCC patients at high risk of postoperative recurrence. This likely reflects the heterogeneity of HCC, so further research is needed to explore factors and treatments that

may reduce postoperative recurrence, as well as factors that may help identify which HCC patients are more likely to benefit from adjuvant treatments such as TACE.

The present study provides evidence for the 1<sup>st</sup> time that CK19 expression may be associated with post-operative prognosis in HCC patients at high recurrent risk. How CK19 might influence post-operative survival and prognosis after TACE is unclear. Based on the expression of CK19, HCC is grouped into non-proliferative and proliferative subtypes. CK19-positive HCC is an aggressive subtype characterized by invasion and angiogenesis, which lead to early tumor recurrence, chemotherapy tolerance, and worse OS [32,33]. The apparent dependence of TACE benefits on CK19 expression may reflect that OS is influenced by many factors that may differ between patients who are positive or negative for CK19, such as location of recurrence and metastasis, body condition, and treatment history. Another possibility is that weak CK19 expression supports the survival benefit of adjuvant TACE, whereas strong expression antagonizes it, perhaps reflecting the association of CK19 with tumor proliferation, angiogenesis,



**Figure 3.** Kaplan-Meier survival curves for patients with hepatocellular carcinoma who underwent hepatic resection and were at high risk of recurrence. (A and B) Overall survival (OS) and recurrence-free survival (RFS) of CK19-positive patients who underwent transarterial chemoembolization (TACE). (C and D) OS and RFS of CK19-negative patients who underwent TACE

**Table 2.** Univariate and multivariate analysis of the overall survival rate of HCC patients with high-risk relapse factors.

Variables	n	Univariate analysis		Multivariate analysis	
		Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P
Male	436	1.216 (0.800-1.847)	0.361	-	-
HCC family history	83	0.867 (0.588-1.277)	0.469	-	-
Age (<60 yrs.)	409	0.999 (0.714-1.398)	0.995	-	-
Ascites	38	1.123 (0.611-2.061)	0.709	-	-
Liver cirrhosis	303	0.950 (0.719-1.255)	0.717	-	-
Alanine aminotransferase (>80 U/L)	69	1.004 (1.002-1.007)	0.002	1.005 (1.001-1.009)	0.026
Aspartate aminotransferase (>80 U/L)	85	1.363 (1.041-1.783)	0.024	1.004 (1.002-1.006)	<0.001
Albumin (>35 g/L)	428	0.943 (0.915-0.972)	<0.001	0.975 (0.941-1.010)	0.162
Prealbumin (<200 mg/L)	489	1.335 (0.628-2.837)	0.453	-	-
Total Bilirubin (>17.1 μmol/L)	116	0.999 (0.719-1.387)	0.994	-	-
Alpha fetoprotein (≥400 ng/ml)	249	1.488 (1.130-1.961)	0.005	1.135 (0.849-1.518)	0.392
HBsAg (+)	430	1.201 (0.806-1.789)	0.369	-	-
Tumor size (≥5 cm)	336	1.419 (1.029-1.957)	0.033	1.764 (1.102-2.825)	0.018
Tumor number≥2	234	0.960 (0.729-1.263)	0.768	-	-
Capsule (incomplete)	81	1.166 (0.806-1.687)	0.414	-	-
Macrovascular invasion	196	3.123 (2.362-4.128)	<0.001	1.507 (1.066-2.130)	0.020
Microvascular invasion	367	1.419 (1.029-1.957)	0.033	1.764 (1.102-2.825)	0.018
Cytokeratin 19 (+)	142	1.609 (1.205-2.148)	0.001	1.519 (1.130-2.042)	0.006
Child-Pugh B	21	1.022 (0.760-1.375)	0.886	-	-
BCLC staging (B/C vs 0/A)	219	3.648 (2.211-6.016)	<0.001	1.760 (0.782-3.959)	0.172
Adjuvant transarterial chemoembolization	202	0.666 (0.499-0.890)	0.006	0.633 (0.472-0.850)	0.002

BCLC: Barcelona clinic liver cancer; HCC, hepatocellular carcinoma

**Table 3.** Univariate and multivariate analysis of the recurrence-free survival rate of HCC patients with high-risk relapse factors.

Variables	n	Univariate analysis		Multivariate analysis	
		Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P
Male	436	1.130 (0.789-1.617)	0.505	-	
HCC family history	83	1.148 (0.841-1.558)	0.385	-	
Age (<60 yrs.)	409	0.987 (0.975-0.988)	0.025	0.987 (0.976-0.999)	0.030
Ascites	38	1.299 (0.824-2.049)	0.260	-	
Liver cirrhosis	303	0.872 (0.687-1.106)	0.259	-	
Alanine aminotransferase (>80 U/L)	69	1.297 (0.928-1.812)	0.128	-	
Aspartate aminotransferase (>80 U/L)	85	1.003 (1.001-1.004)	0.004	1.002 (1.000-1.004)	0.074
Albumin (>35 g/L)	428	0.975 (0.952-0.999)	0.044	0.975 (0.950-1.001)	0.062
Prealbumin (<200 mg/L)	489	1.350 (0.718-2.539)	0.351	-	
Total Bilirubin (>17.1 μmol/L)	116	1.089 (0.823-1.441)	0.552	-	
Alpha fetoprotein (ng/ml)	249	1.436 (1.137-1.813)	0.002	1.323 (1.039-1.685)	0.023
HBsAg (+)	430	1.027 (0.741-1.423)	0.873	-	
Tumor size (≥5 cm)	336	1.658 (1.284-2.142)	<0.001	1.286 (0.970-1.704)	0.080
Tumor number≥2	234	1.229 (0.975-1.551)	0.081	-	
Capsule (incomplete)	81	1.109 (0.820-1.501)	0.501	-	
Macrovascular invasion	196	1.857 (1.462-2.360)	<0.001	1.004 (0.683-1.476)	0.983
Microvascular invasion	367	0.902 (0.702-1.160)	0.422	-	
Cytokeratin 19 (+)	142	1.376 (1.065-1.777)	0.014	1.392 (1.068-1.813)	0.014
Child-Pugh B	21	1.042 (0.584-1.859)	0.889	-	
BCLC staging (B/C vs. 0/A)	219	1.589 (1.358-1.860)	<0.001	1.436 (1.114-1.849)	0.005
Adjuvant transarterial chemoembolization	202	0.643 (0.507-0.814)	<0.001	0.575 (0.451-0.733)	<0.001

BCLC: Barcelona clinic liver cancer; HCC: Hepatocellular carcinoma

invasiveness, metastasis, and treatment resistance [34]. In the present study, weak and strong expression were classified together as “positive” because of the small number of patients, so a finer classification may reveal more insight into the relationship between CK19 expression and TACE benefit.

The results should be interpreted with caution given that the study was relatively small, retrospective, and limited to a single center. Nevertheless, the results provide evidence that adjuvant TACE can confer survival value, but not necessarily in the presence of strong CK19 expression. Improvements to TACE may increase benefits for a broader range of patients. For example, performing TACE with hypersphere drug-loaded microspheres rather than iodized oil emulsifiers may reduce the risk of adverse reactions during and after the procedure, as well as accelerate liver recovery [35,36]. Another possibility is combined therapies (TACE combined with radiofrequency ablation or lenvatinib), which may be better than TACE alone because lenvatinib can inhibit the activity of vascular endothelial growth factor produced in response to TACE-induced tumor hypoxia [37].

The results may help guide decision-making about adjuvant TACE in HCC patients at high risk of recurrence. The technique appears to be beneficial for most CK19-negative patients, but it may be less effective for CK19-positive patients, for whom comprehensive adjuvant therapies such as targeted therapy and immunotherapy may be better for improving OS [38,39]. These findings should be verified and extended in large, prospective studies.

## 5. Conclusion

In conclusion, the results of this study indicated that adjuvant TACE can significantly prolong OS and RFS of CK19-negative HCC patients at high risk of recurrence after hepatic resection, while it may prolong only RFS of CK19-positive patients. CK19-positivity is an independent risk factor for poor prognosis of HCC. For CK19-positive HCC patients, more emphasis should be placed on comprehensive adjuvant therapies after hepatic resection in order to improve OS.

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## Conflict of Interest

The authors declare no conflict of interest.

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