Adjuvant Transarterial Chemoembolization does not Influence Recurrence-free and Overall survivals for Patients with Combined Hepatocellular Carcinoma and Cholangiocarcinoma after Curative Resection: a Propensity Score Matching Analysis

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Abstract

Background : The prognosis of patients with combined hepatocellular carcinoma and intrahepatic cholangiocarcinoma (CHC) is usually poor, and effective adjuvant therapy is ineffective making it important to investigate whether these patients may benefit from adjuvant transarterial chemoembolization (TACE). We aimed to evaluate the efficiency of adjuvant TACE for long-term recurrence and survival after curative resection before and after propensity score matching (PSM) analysis. Methods : In this retrospective study, of 230 patients who underwent resection for CHC between January 1994 and December 2014, 46 (18.0%) patients received adjuvant TACE. Univariate and multivariate regression analyses were used to identify the independent predictive factors of survival. Cox regression analyses and log-rank tests were used to compare overall survival (OS) and disease-free survival (DFS) between patients who did or did not receive adjuvant TACE. Results : A total of 230 patients (mean age 52.2±11.9 years; 172 men) were enrolled, and 46 (mean age 52.7±11.1 years; 38 men) patients received TACE. Before PSM, in multivariate regression analysis, γ-glutamyl transpeptidase (γ-GT), tumour nodularity, macrovascular invasion (MVI), lymphoid metastasis, and extrahepatic metastasis were associated with OS. Alanine aminotransferase (ALT), MVI, lymphoid metastasis, and preventive TACE (HR: 2.763, 95% CI: 1.769-4.314, p <0.001) were independent prognostic factors for DFS. PSM created 46 pairs of patients. After PSM, adjuvant preventive TACE was not associated with an increased risk of OS (HR: 0.911, 95% CI: 0.545-1.520, p =0.720) or DFS (HR: 3.345, 95% CI: 1.686-6.638, p =0.001). After PSM, the 5-year OS and DFS rates were comparable in the TACE group and the non-TACE group (OS: 22.7% vs 14.9%, respectively, p =0.75; DFS: 11.2% vs 14.4%, respectively, p =0.06). Conclusions : The present study identified that adjuvant preventive TACE did not influence DFS or OS after curative resection of CHC.

Background

Primary liver cancer (PLC) is a heavy global health burden; it ranks as the second leading cause of mortality in men in less-developed countries, especially in China, which accounts for more than 50% of PLC patients in the world [1, 2]. PLC is composed of several biologically distinct subtypes: hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and combined hepatocellular-cholangiocarcinoma (CHC). As a distinct and rare subtype of PLC, CHC accounts for less than 5% of PLC cases, with histological evidence of both hepatocellular and biliary epithelial differentiation [3, 4]. Due to the stem cell features of CHC, this disease is associated with an aggressive course and a poor prognosis, with 5-year overall survival (OS) ranging from 9.2%-40% [5, 6].

Effective treatments for CHC are deficient. In our previous study, we found that radical surgical resection provided a better outcome that was intermediate between HCC and ICC [7, 8]. Aggressive surgical treatment, including lymph node dissection, may improve survival in patients diagnosed with CHC [9]. Regardless of Allen and Lisa class or the predominance of ICC cells within the tumour, the 5-year OS rate is 24% after hepatectomy [10]. Liver transplantation is not an appropriate therapeutic choice for CHC due to the disappointing results, with a mean OS of 11.7 months and a mean disease-free survival (DFS) of

7.97 months [11]. However, a group reported that very early CHC resulted in favourable posttransplant prognosis [12]. However, these studies had relatively small sample sizes and were retrospective in nature.

Similar to HCC and ICC, for CHC, recurrence is the most adverse factor influencing OS and DFS; vascular and lymph node invasion as well as the presence of satellite metastasis have been suggested as significant predictors of poor outcome after curative resection [13–15]. Transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA) are the most widely used treatments for HCC and postresection recurrence [16–18]. For CHC, TACE shows an advantageous response and prognosis in recurrent patients after resection [19]. TACE is effective for prolonging the survival of patients with nonresectable CHC. Nonetheless, the effect of adjuvant TACE in CHC patients after curative resection is still unknown.

To address this issue, we conducted a retrospective cohort study to elucidate the relationship between adjuvant TACE and long-term recurrence and survival after curative resection of CHC using propensity score matching (PSM) and multivariate Cox regression analyses.

Methods

Participants and criteria

This was a retrospective study that used data collected at a single medical centre. The study was approved by the institutional review board and was in accordance with the standards of the Declaration of Helsinki and current ethical guidelines. Written informed consent was obtained for each patient. The inclusion and exclusion criteria are presented in the supplemental information.

Between January 1994 and December 2014, a total of 255 patients who underwent curative hepatic resection and were diagnosed with CHC in the Department of Liver Surgery were retrospectively enrolled in this study. Among them, 25 patients who received preoperative surgery and anticancer treatments were excluded: sixteen patients with a previous history of surgery, 2 patients who received preoperative TACE, and 7 patients with missing data. Thus, 230 patients were enrolled in the final analyses (Fig. 1). The detailed criteria for curative resection are shown in the supplemental information [20].

TACE

The risk of recurrence after resection was assessed by tumour characteristics, which were established by the pathology report, and the patients with intermediate or high risks of recurrence were advised to undergo TACE therapy. A high risk of recurrence was defined as a single tumour with microvascular invasion or two or three tumours, and an intermediate risk of recurrence was defined as a solitary tumour larger than 5 cm without microvascular invasion [16, 21]. Using the Seldinger technique, a vascular catheter was inserted through a femoral artery to the hepatic artery, and hepatic angiography was then carried out. A microcatheter was used to inject Adriamycin (20–30 mg/m^2) and lipiodol (3–5 mL) into the left and right hepatic arteries.

Follow-up

Patients were followed in our centre every 3 months until death or dropout from the follow-up programme. The detailed follow-up procedures are shown in the supplemental information.

Variables And Outcomes

The data were prospectively collected and retrospectively reviewed. The detailed information from the database is shown in the supplemental information. The main outcomes of this study were OS and DFS. OS was measured from the date of the resection to either the date of death of the date of the last follow-up. DFS was defined from the date of the resection to the date of first recurrence or the date of death or the last follow-up visit.

PSM

Patients in the TACE and non-TACE groups were matched using the PSM method [22], which was carried out using R software version 2.10.0 (R Project for Statistical Computing, https://www.r-project.org/, New Zealand). First, a propensity score (from 0 to 1) that contained the information of variates that was selected during matching was generated by logistic regression in PSM. Then, to create a reliable propensity score model, the variables that were chosen for matching included all the potential confounders [23, 24]. Thus, the variables contained all the independent prognostic factors of CHC. The Cox proportional hazards model was used to identify the independent prognostic factors, and the variables with statistical significance ($p < 0.25$) in univariate analysis were entered into multivariate analysis. The variables entered into the final propensity model were sex, ALT, perioperative blood transfusion, and lymphoid metastasis. Then, the model used one-to-one matching without replacement between TACE and non-TACE patients by using the nearest-neighbour matching algorithm. The calliper value was selected as 0.01, and the balance between the two groups after matching was evaluated by the standardized mean difference ($p < 0.1$).

Statistical analysis

Statistical analyses were carried out using IBM SPSS 22.0 (SPSS Inc., Armonk, NY, USA) and SASS 9.1 (SAS Institute Inc., Cary, NC, USA). The demographic, clinical, and tumour characteristics were documented as summary statistics that were obtained using established methods. In both the TACE and non-TACE groups, continuous data were presented as the mean with a 25th -75th percentile range and analysed using Student's t test or the Mann-Whitney U test. The categorical variables were presented as absolute and relative frequencies and compared by Pearson's χ^2 analysis or Fisher's exact test. OS and DFS were compared using the Kaplan-Meier method, and survival differences between the two groups were analysed using the log-rank test. Multivariate Cox proportional hazard regression analyses were then carried out to adjust for other prognostic factors that were associated with OS and DFS. Moreover, to strengthen the accuracy of the model, a robust sandwich variance estimator was used in all the cohorts

for estimating the hazard ratios and their 95% confidence intervals (CIs). All tests using two-tailed $p < 0.05$ were considered to be statistically significant.

Results

Demographic and clinicopathological characteristics

Table 1 summarizes the baseline characteristics of patients with CHC who underwent TACE (n = 46) and those who did not (n = 184) before PSM. The mean age of patients in the TACE group (52 ± 10.7 years) was similar to that of patients in the non-TACE group (52.3 ± 12.1 years), and the sex distribution was similar in both groups (38 and 134 male patients in the TACE group and non-TACE group, respectively). The median AFP ($p = 0.006$), median bilirubin ($p < 0.001$), occlusion time ($p = 0.044$), and macrovascular invasion ($p = 0.041$) were higher in the TACE group than in the non-TACE group, and the median CA199 was higher in the non-TACE group than in the TACE group ($p = 0.029$). After PSM, the mean age of patients in the TACE group (52 ± 10.7 years) was similar to that of patients in the non-TACE group (53.4 ± 11.6 years), and the sex distribution was similar in both groups. Except for the higher median AFP ($p = 0.002$) and lower median CA199 ($p = 0.023$) in the TACE group, there were no significant differences between the TACE group and the non-TACE group in terms of the baseline characteristics ($p > 0.05$).

Table 1

Preoperative clinicopathologic Data of Patients with CHC Who received or not postoperative TACE.

Variable	Before Propensity Matching			After Propensity Matching		
	Without TACE (n = 184)	Postoperative TACE (n = 46)	P	Without TACE (n = 46)	Postoperative TACE (n = 46)	P
Sex			0.172			> 0.99
Men	134	38		38	38	
Women	50	8		8	8	
Mean age (y)	52.3 ± 12.1	52 ± 10.7	0.326	53.4 ± 11.6	52 ± 10.7	0.834
HBsAg			> 0.99			0.810
Positive	136	34		35	34	
Negative	48	12		11	12	
HBcAb			0.666			0.231
Positive	153	9		42	9	
Negative	31	37		4	37	
HCV antibody			> 0.99			> 0.99
Positive	4	1		1	1	
Negative	180	45		45	45	
Median AFP, ng/mL	24.7 (1-80000)	96 (1.8-46897)	0.006	21.3 (1-30728)	96 (1.8-46897)	0.002
Median CEA, μg/mL	2.5 (0-274)	2.1 (0.5–70.5)	0.364	2.7 (0.1-112.4)	2.1 (0.5–70.5)	0.423
Median CA19-9, U/ml	28.1 (0-4370)	19.4 (0.2-300.1)	0.029	22 (0.5-4062.5)	19.4 (0.2-300.1)	0.023
Median bilirubin, μmol/L	11.8 (1.7-314.8)	12.9 (5.7-156.5)	< 0.001	13.7 (2.4-169.3)	12.9 (5.7-156.5)	0.664
Median albumin, g/L	41 (26–55)	42 (35–66)	0.397	41 (30–48)	42 (35–66)	0.556
Median ALT, U/L	28 (5-484)	31 (5-104)	0.094	26 (11–484)	31 (5-104)	0.109

Variable	Before Propensity Matching			After Propensity Matching		
	Without TACE (n = 184)	Postoperative TACE (n = 46)	P	Without TACE (n = 46)	Postoperative TACE (n = 46)	P
Median ALP, IU/L	89.5 (22-1413)	88.5 (46–184)	0.477	92 (25–331)	88.5 (46–184)	0.599
Median GGT, U/L	59 (3.6–1632)	80 (18–490)	0.923	75.5 (10–658)	80 (18–490)	0.273
Median platelets, 10^3/μL	13.7 (2.2–47.6)	16 (3.9–46.1)	0.319	15.3 (5.3–24.7)	16 (3.9–46.1)	0.171
Median prothrombin time, s	11.8 (9-17.6)	12 (10.2–13.8)	0.941	12 (10.2–14.6)	12 (10.2–13.8)	0.903
Median INR	1 (0.5–1.5)	1 (0.8–1.2)	0.227	1 (0.5–1.2)	1 (0.8–1.2)	0.065
Median tumour size, cm	5 (1–24)	7.3 (1.5–17)	0.626	6 (1.5–22)	7.3 (1.5–17)	0.384
Median tumour nodularities	1 (1–10)	1 (1–5)	0.140	1 (1–6)	1 (1–5)	0.648
Median blood loss, ml	200 (30-3500)	200 (10-2500)	0.182	200 (50-1800)	200 (10-2500)	0.480
Mean occlusion, min	6.8 ± 8.6	10 ± 1.6	0.044	5.4 ± 1.1	10 ± 1.6	0.090
Macrovascular invasion			0.041			> 0.99
Positive	11	7		7	7	
Negative	173	39		39	39	
Microvascular invasion			0.689			0.607
Positive	39	11		8	11	
Negative	145	35		38	35	
Lymphoid metastasis			0.840			> 0.99
Positive	22	6		6	6	
Negative	162	40		40	40	

Variable	Before Propensity Matching			After Propensity Matching		
	Without TACE (n = 184)	Postoperative TACE (n = 46)	P	Without TACE (n = 46)	Postoperative TACE (n = 46)	P
Extrahepatic metastasis			0.719			0.646
Positive	6	2		3	2	
Negative	178	44		43	44	

Os And Dfs Before Psm

The median survival of the whole cohort was 22.6 months, and the overall cumulative OS rates at 1, 3, 5, and 10 years were 48.5%, 33.3%, 25.8%, and 15.3%, respectively. The median OS of the TACE group and non-TACE group was 22.0 months and 23.5 months, respectively. The cumulative OS rates were comparable between the two groups; the 1-, 3-, 5-, and 10-year OS rates in the TACE group were 46.6%, 31.7%, 22.7%, and 12.6%, respectively, whereas those in the non-TACE group were 49.0%, 33.7%, 26.6%, and 16.1%, respectively ($p = 0.34$) (Fig. 2A). The median DFS of the whole cohort was 14.0 months, and the cumulative DFS rates at 1, 3, 5, and 10 years were 20.9%, 10.4%, 0.7%, and 0.3%, respectively. Stratified by TACE, the median DFS in the TACE group was less than that in the non-TACE group (9.3 months vs. 17.2 months) ($p = 0.001$) (Fig. 2B).

The Prognostic Factors Of Chc Before Psm

To identify potential confounders, we used the Cox proportional hazards model to analyse the risk factors for CHC. For OS, in univariate analysis, the following six variants were enrolled in the multivariate analysis: γ-GT ($p < 0.001$), tumour size ($p = 0.002$), tumour nodularities ($p = 0.003$), macrovascular invasion ($p < 0.001$), lymphoid metastasis ($p < 0.001$), and extrahepatic metastasis ($p < 0.001$). In multivariate analysis, γ-GT ($p = 0.001$), tumour nodularities ($p = 0.031$), macrovascular invasion ($p < 0.001$), lymphoid metastasis ($p = 0.008$), and extrahepatic metastasis ($p < 0.001$) were independent factors of OS (Table 2).

Table 2

Univariable and multivariable cox analysis of OS before propensity matched analysis

Variable	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Age (≥ 60/<60, year)	1.279	0.857–1.908	0.229	—	—	—
Sex (Men/Women)	1.443	0.95–2.193	0.085	—	—	—
HBsAg (yes/no)	1.044	0.719–1.517	0.821	—	—	—
HCV antibody (yes/no)	2.293	0.722–7.283	0.159	—	—	—
AFP (≥ 20/<20, ng/mL)	2.819	0.68-11.682	0.153	—	—	—
CEA (≥ 5/□5, ng/mL)	1.844	0.643–5.29	0.255	—	—	—
CA19-9 (≥ 37/□37, U/mL)	2.069	0.639–6.702	0.225	—	—	—
Liver cirrhosis, yes (%)	1.252	0.857–1.83	0.245	—	—	—
TB (≥ 17/<17, μmol/L)	0.950	0.626–1.443	0.810	—	—	—
ALB (≥ 40/□40, g/mL)	0.759	0.530–1.086	0.132	—	—	—
ALT (≥ 35/□35, U/L)	1.327	0.941–1.870	0.106	—	—	—
γ-GT (≥ 40/□40, U/L)	2.662	1.703–4.163	< 0.001	2.152	1.354–3.421	0.001
PLT (≥ 10/<10 10^3/μL)	1.005	0.665–1.518	0.982	—	—	—
Prothrombin time, median (range), s	1.199	0.781–1.841	0.406	—	—	—
Tumour size, cm	1.769	1.235–2.534	0.002	1.274	0.867–1.872	0.218
Tumour nodularities	1.167	1.055–1.292	0.003	1.130	1.011–1.262	0.031
Occlusion, min (< 20/≥20)	0.290	0.740–2.250	0.369	—	—	—

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcino-embryonic antigen; CA19-9, carbohydrate 19 – 9; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transpeptidase; PLT, platelet; ALP, alkaline phosphatase; NS, non-sense.

Variable	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Macrovascular invasion (yes/no)	1.927	1.442–2.576	< 0.001	1.869	1.375–2.540	< 0.001
Microvascular invasion (yes/no)	1.365	0.921–2.204	0.122	—	—	—
Lymphoid metastasis (yes/no)	2.801	1.745–4.495	< 0.001	2.031	1.201–3.435	0.008
Extrahepatic metastasis (yes/no)	11.435	5.262–24.849	< 0.001	6.392	2.731–14.961	< 0.001
Preventive TACE (yes/no)	1.212	0.807–1.821	0.354	—	—	—

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcino-embryonic antigen; CA19-9, carbohydrate 19 – 9; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transpeptidase; PLT, platelet; ALP, alkaline phosphatase; NS, non-sense.

For DFS, in univariate analysis, the following five variants were enrolled in the multivariate analysis: male sex ($p = 0.034$), ALT ($p = 0.008$), γ-GT ($p = 0.016$), occlusion time ($p = 0.002$), macrovascular invasion ($p = 0.001$), lymphoid metastasis ($p = 0.005$), and preventive TACE ($p < 0.001$). In multivariate analysis, we found that ALT ($p = 0.031$), macrovascular invasion ($p = 0.001$), lymphoid metastasis ($p = 0.001$), and preventive TACE (HR: 2.763, 95% CI: 1.769–4.314, $p < 0.001$) were independent prognostic factors of DFS (Table 3).

Table 3

Univariable and multivariable cox analysis of DFS before propensity matched analysis

Variable	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Age (≥ 60/<60, year)	1.240	0.765–2.010	0.382	—	—	—
Sex (Men/Women)	1.751	1.042–2.941	0.034	1.919	1.097–3.357	0.022
HBsAg (yes/no)	0.672	0.405–1.114	0.123	—	—	—
HCV antibody (yes/no)	0.782	0.108–5.636	0.807	—	—	—
AFP (≥ 20/<20, ng/mL)	1.245	0.824–1.881	0.299	—	—	—
CEA (≥ 5/<5, ng/mL)	1.169	0.672–2.035	0.581	—	—	—
CA19-9 (≥ 37/<37, U/mL)	1.136	0.727–1.775	0.575	—	—	—
Liver cirrhosis, yes (%)	1.291	0.815–2.044	0.277	—	—	—
TB (≥ 17/<17, μmol/L)	0.998	0.607–1.641	0.995	—	—	—
ALB (≥ 40/<40, g/mL)	0.771	0.499–1.191	0.241	—	—	—
ALT (≥ 35/<35, U/L)	1.741	1.154–2.267	0.008	1.676	1.050–2.677	0.031
γ-GT (≥ 40/<40, U/L)	1.811	1.116–2.938	0.016	1.105	0.653–1.870	0.711
PLT (≥ 10/<10 10^3/μL)	0.856	0.529–1.382	0.524	—	—	—
Prothrombin time, median (range), s	1.417	0.845–2.375	0.186	—	—	—
Tumour size, cm	1.226	0.809–1.857	0.338	—	—	—

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcino-embryonic antigen; CA19-9, carbohydrate 19 – 9; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transpeptidase; PLT, platelet; ALP, alkaline phosphatase; NS, non-sense.

Variable	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Tumour nodularities	1.056	0.918–1.215	0.442	—	—	—
Occlusion, min (< 20/≥20)	2.363	1.356–4.119	0.002	1.790	0.974–3.289	0.061
Macrovascular invasion (yes/no)	1.878	1.300-2.713	0.001	2.026	1.342–3.058	0.001
Microvascular invasion (yes/no)	1.084	0.654–1.797	0.754	—	—	—
Lymphoid metastasis (yes/no)	2.300	1.287–4.112	0.005	2.835	1.517–5.297	0.001
Extrahepatic metastasis (yes/no)	2.248	0.538–9.395	0.267	—	—	—
Preventive TACE (yes/no)	2.799	1.815–4.317	< 0.001	2.763	1.769–4.314	< 0.001

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcino-embryonic antigen; CA19-9, carbohydrate 19 – 9; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transpeptidase; PLT, platelet; ALP, alkaline phosphatase; NS, non-sense.

Psm For Tace And Non-tace Patients

The distribution of the risk factors and demographic characteristics differed between the TACE and non-TACE groups. To reduce confounding factors and to reflect the true effect of TACE, we established a PSM model based on the analysis of the risk factors described above. Considering OS and DFS, four variates were involved in the model: AFP, CA19-9, total bilirubin, and macrovascular invasion. Finally, we matched 46 pairs of TACE and non-TACE patients. Apart from AFP, all other variables were balanced between the two groups (all $p > 0.2$). The balances between the two groups are shown in Table 1.

Os And Dfs After Psm

After PSM, the median OS of the TACE group and non-TACE group was 22.0 months and 16.3 months, respectively. The cumulative survival rates in the TACE group at 1, 3, 5, and 10 years were 46.6%, 31.7%, 22.7%, and 12.6%, respectively, whereas those in the non-TACE group were 36.4%, 22.4%, 14.9%, and 14.9%, respectively. However, the OS between the TACE and non-TACE groups was still comparable after PSM ($p = 0.75$) (Fig. 2C). The median DFS of the TACE group and non-TACE group was 7.3 months and 10.0 months, respectively. The cumulative DFS rates in the TACE group at 1, 3, 5, and 10 years were 20.8%, 14.9%, 11.2%, and 5.6%, respectively, whereas those in the non-TACE group were 28.7%, 14.4%,

14.4%, and 14.4%, respectively. However, the DFS between the TACE and non-TACE groups was comparable after PSM ($p = 0.06$) (Fig. 2D).

The Prognostic Factors Of Chc After Psm

After PSM, for OS, in univariate analysis, the following three variants were enrolled in the multivariate analysis: HCV antibody ($p = 0.013$), macrovascular invasion ($p < 0.001$), and extrahepatic metastasis ($p < 0.001$). In multivariate analysis, HCV antibody ($p = 0.004$), macrovascular invasion ($p = 0.001$), and extrahepatic metastasis ($p < 0.001$) were independent factors of OS (Table 4).

Table 4

Univariable and multivariable cox analysis of OS after propensity matched analysis

Variable	Univariable			Univariable		
	HR	95% CI	P	HR	95% CI	P
Age (≥ 60/<60, year)	0.922	0.463–1.837	0.818	—	—	—
Sex (Men/Women)	1.458	0.689–3.087	0.324	—	—	—
HBsAg (yes/no)	1.711	0.887-3.300	0.109	—	—	—
HCV antibody (yes/no)	6.405	1.491–27.524	0.013	9.142	2.028–41.225	0.004
AFP (≥ 20/<20, ng/mL)	1.288	0.761–2.181	0.346	—	—	—
CEA (≥ 5/□5, ng/mL)	1.643	0.924–2.923	0.091	—	—	—
CA19-9 (≥ 37/□37, U/mL)	1.591	0.932–2.715	0.089	—	—	—
Liver cirrhosis, yes (%)	1.952	1.091–3.493	1.379	6.264	0.734–2.590	0.318
TB (≥ 17/<17, μmol/L)	0.739	0.383–1.427	0.368	—	—	—
ALB (≥ 40/□40, g/mL)	0.814	0.476–1.391	0.451	—	—	—
ALT (≥ 35/□35, U/L)	1.459	0.869–2.452	0.153	—	—	—
γ-GT (≥ 40/□40, U/L)	1.811	0.933–3.515	0.079	—	—	—
PLT (≥ 10/<10 10^3/μL)	1.353	0.683–2.682	0.386	—	—	—
Prothrombin time, median (range), s	1.014	0.547–1.880	0.964	—	—	—
Tumour size, cm	1.466	0.814–2.639	0.203	—	—	—
Tumour nodularities	1.017	0.785–1.318	0.898	—	—	—

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcino-embryonic antigen; CA19-9, carbohydrate 19 – 9; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transpeptidase; PLT, platelet; ALP, alkaline phosphatase; NS, non-sense.

Variable	Univariable			Univariable		
	HR	95% CI	P	HR	95% CI	P
Occlusion, min (< 20/≥20)	1.560	0.735–3.310	0.247	—	—	—
Macrovascular invasion (yes/no)	3.343	1.770–6.315	< 0.001	3.035	1.543–5.972	0.001
Microvascular invasion (yes/no)	1.359	0.725–2.546	0.338	—	—	—
Lymphoid metastasis (yes/no)	1.487	0.667–3.315	0.332	—	—	—
Extrahepatic metastasis (yes/no)	6.805	2.549–18.166	< 0.001	6.264	2.277–17.235	< 0.001
Preventive TACE (yes/no)	0.911	0.545–1.520	0.720	—	—	—

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcino-embryonic antigen; CA19-9, carbohydrate 19 − 9; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transpeptidase; PLT, platelet; ALP, alkaline phosphatase; NS, non-sense.

Table 5

Univariable and multivariable cox analysis of DFS after propensity matched analysis

Variable	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Age (≥ 60/<60, year)	1.198	0.587–2.443	0.620	—	—	—
Sex (Men/Women)	1.827	0.713–4.685	0.209	—	—	—
HBsAg (yes/no)	1.478	0.706–3.096	0.300	—	—	—
HCV antibody (yes/no)	0.048	0.526–4.934	0.665	—	—	—
AFP (≥ 20/<20, ng/mL)	1.075	0.585–1.976	0.815	—	—	—
CEA (≥ 5/<5, ng/mL)	0.820	0.380–1.771	0.614	—	—	—
CA19-9 (≥ 37/<37, U/mL)	1.019	0.520–1.997	0.957	—	—	—
Liver cirrhosis, yes (%)	1.436	0.752–2.744	0.273	—	—	—
TB (≥ 17/<17, μmol/L)	0.941	0.449–1.973	0.873	—	—	—
ALB (≥ 40/<40, g/mL)	0.580	0.315–1.068	0.080	—	—	—
ALT (≥ 35/<35, U/L)	2.083	1.120–3.873	0.020	1.989	0.980–4.037	0.057
γ-GT (≥ 40/<40, U/L)	1.265	0.616–2.597	0.521	—	—	—
PLT (≥ 10/<10 10^3/μL)	0.975	0.466–2.043	0.947	—	—	—
Prothrombin time, median (range), s	1.841	0.942–3.598	0.074	—	—	—
Tumour size, cm	1.077	0.560–2.071	0.823	—	—	—

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcino-embryonic antigen; CA19-9, carbohydrate 19 – 9; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transpeptidase; PLT, platelet; ALP, alkaline phosphatase; NS, non-sense.

Variable	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Tumour nodularities	0.992	0.731–1.346	0.957	—	—	—
Occlusion, min (< 20/≥20)	3.308	1.388–6.647	0.005	1.565	0.639–3.833	0.327
Macrovascular invasion (yes/no)	3.703	1.607–8.535	0.002	3.361	1.416–7.977	0.006
Microvascular invasion (yes/no)	1.705	0.854–3.407	0.131	—	—	—
Lymphoid metastasis (yes/no)	1.423	0.553–3.663	0.464	—	—	—
Extrahepatic metastasis (yes/no)	2.246	0.520–9.712	0.279	—	—	—
Preventive TACE (yes/no)	3.144	1.610–6.137	0.001	3.345	1.686–6.638	0.001

HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, α-fetoprotein; CEA, carcino-embryonic antigen; CA19-9, carbohydrate 19 – 9; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; γ-GT, γ-glutamyl transpeptidase; PLT, platelet; ALP, alkaline phosphatase; NS, non-sense.

For DFS, in univariate analysis, the following four variants were enrolled in the multivariate analysis: ALT (p = 0.02), occlusion time (p = 0.005), macrovascular invasion (p = 0.002), and preventive TACE (p = 0.001). In multivariate analysis, macrovascular invasion (p = 0.006) and preventive TACE (HR: 3.345, 95% CI: 1.686–6.638, p = 0.001) were independent factors of DFS.

Discussion

CHC is a rare and complex disease with limited treatment options. In our previous study, we constructed a convenient and reliable prediction model for identifying individuals with CHC. In this model, 2.73% of the patients diagnosed with liver cancer were definitely diagnosed with CHC [6]. However, even with curative resection, the prognosis of CHC is dismal. Due to its more malignant behaviour than HCC and ICC, CHC tends to recur after curative resection [25]. Herein, we answered this difficult question: can we prolong the survival of CHC patients after curative resection? We found that postoperative adjuvant TACE could not prolong DFS in CHC patients after curative resection.

Regarding HCC recurrence, many postoperative adjuvant therapies, including targeted therapy, have reported limited success [20, 26, 27]. In our previous retrospective study, postoperative adjuvant TACE prolonged the survival of patients with risk factors [28, 29]. In our prospective study, we found that adjuvant TACE significantly reduced tumour recurrence and improved RFS and OS in patients with HBV-

related HCC who had an intermediate or high risk for recurrence [16]. Regarding ICC recurrence, ICC patients with high nomogram scores benefited from adjuvant TACE following liver resection [30].

In CHC management, TACE is considered to be inefficient, as CHC has less vasculature and is much more fibrotic than HCC [31]. However, one study showed that TACE was effective for prolonging the survival of patients with nonresectable CHC, and the survival period after TACE was dependent on tumour size, tumour vascularity, liver function, and the presence or absence of portal vein invasion [32]. According to the enhanced pattern, the globally enhancing type showed a better response and prognosis after TACE than the peripherally enhancing type [19]. In our view, as CHC is less vascular and much more fibrotic than HCC, thus CHC is less likely to respond to TACE [31], which may contribute to the inefficiency of postoperative adjuvant TACE in CHC patients.

This study has several limitations. First, this is a retrospective cohort study but not a randomized controlled trial. However, due to the rare incidence of CHC, it is nearly impossible to perform a randomized trial. As was done in the present study, it is the best-suited study design to apply PSM and multivariate Cox regression analyses. Second, our study is based on a single institution, and external confirmation is urgently needed in our future work. Third, the HBV rate was higher than the rates published from Western countries, which may cause bias in clinical decision-making. Finally, we found that adjuvant TACE shortened DFS and did not affect OS in CHC patients, as OS and DFS were influenced by tumour characteristics and treatment modalities. Whether adjuvant TACE affects OS and DFS also needs further investigation.

Conclusions

To summarize, with the use of propensity score analyses and multivariate Cox regression analyses, our present study showed that adjuvant TACE shortened DFS and did not affect OS in CHC patients. Our study showed that more specific criteria, such as tumour enhancement type, should be warranted for select patients who will benefit from postoperative adjuvant TACE.

Abbreviations

AFP: α-fetoprotein; ALP, alkaline phosphatase; ALT: alanine aminotransferase; CA19-9, carbohydrate 19-9; CEA, carcino-embryonic antigen; CHC: combined hepatocellular carcinoma and intrahepatic cholangiocarcinoma; CI: confidence interval; DFS: disease-free survival; γ-GT: γ-glutamyl transpeptidase; HBcAb, hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCV, hepatitis C virus; HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; INR, International normalized ratio; MVI, vascular invasion; OS: overall survival; PEI: percutaneous ethanol injection; PLC: primary liver cancer; PSM: propensity score matching; RFA: radiofrequency ablation; TACE: transarterial chemoembolization.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of the Zhongshan Hospital, Fudan University. Written informed consents were obtained from each patient.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and design: J Zhou, J Fan, YH Shi; Administrative support: Zhou, J Fan, YH Shi; Provision of study materials or patients: All authors; Collection and assembly of data: WR Liu, MX Tian, CY Tao, Z Tang, Y Fang, YF Zhou, SS Song, XF Jiang, H Wang, PY Zhou, WF Qu, ZB Ding, J Zhou, J Fan, YH Shi; Data analysis and interpretation: WR Liu, MX Tian, J Zhou, J Fan, YH Shi; Manuscript writing: WR Liu, J Fan, YH Shi; Final approval of manuscript: All authors.

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Figures

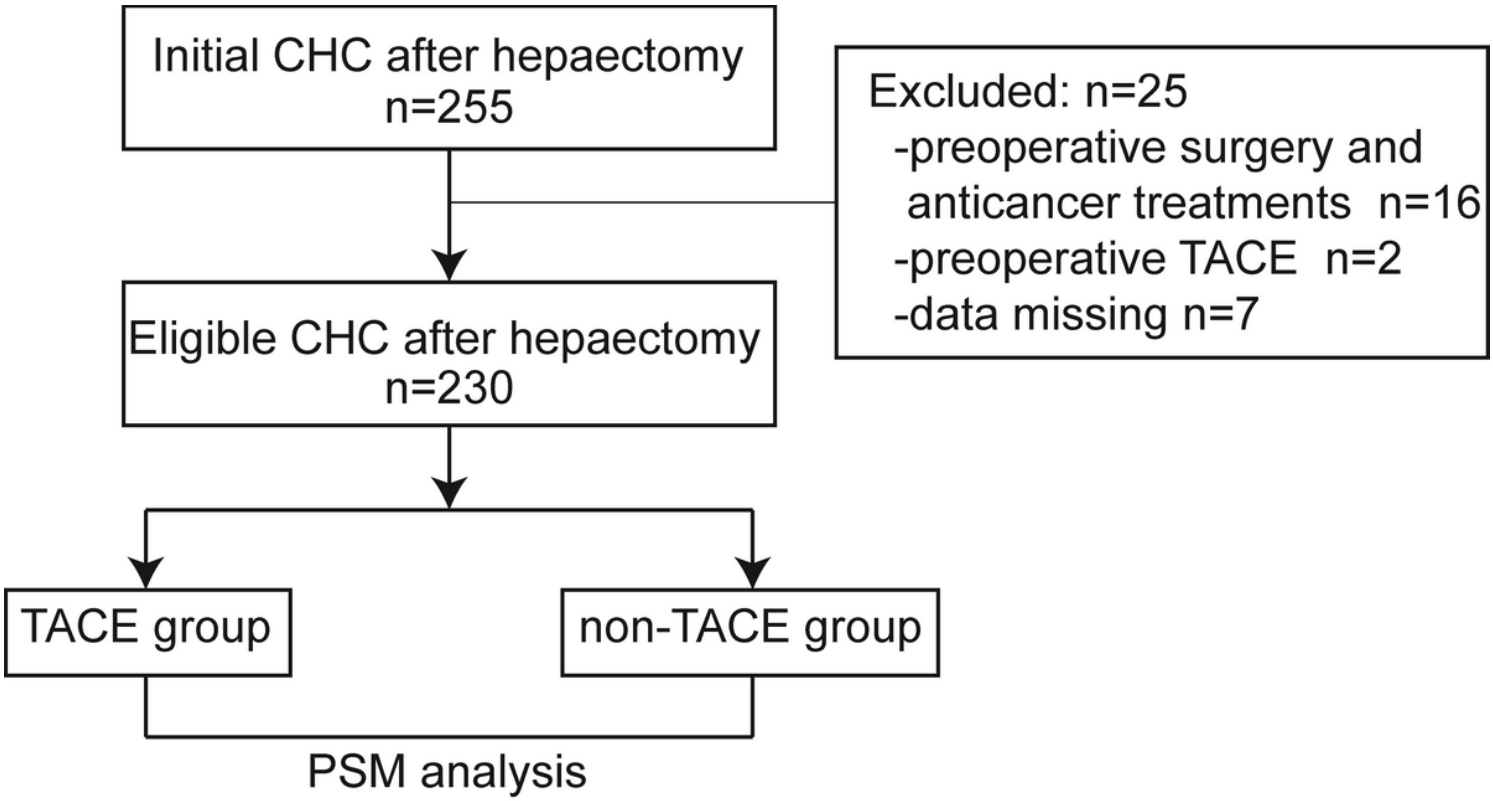

Figure 1

patients enrolled in the final analyses

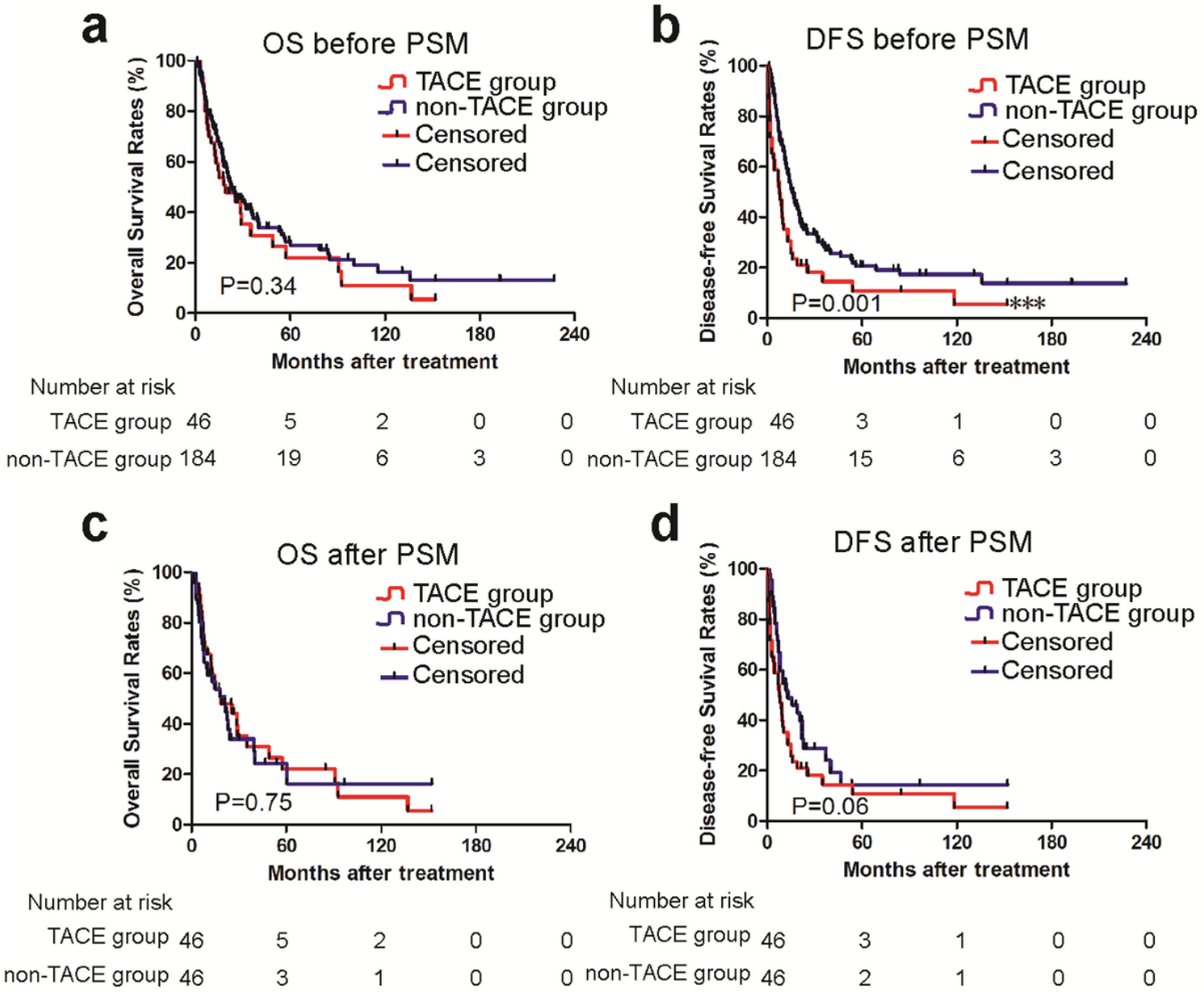

Figure 2

OS and DFS before PSM

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