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RESEARCH

Prognostic analysis and limited efficacy of adjuvant TACE in hepatocellular carcinoma following hepatectomy: a propensity score-matched study

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Abstract

Background Postoperative adjuvant transarterial chemoembolization (PA-TACE) is proposed as a potentially effective treatment for hepatocellular carcinoma (HCC), but its benefits may be limited according to recent evidence.

Methods We analyzed clinicopathologic data from HCC patients who underwent hepatectomy between 2014 and 2019, categorizing them into two groups: surgery alone (non-PA-TACE) and PA-TACE. Propensity score matching (PSM) was used to adjust for selection bias. Cox proportional hazard models identified independent prognostic factors for overall survival (OS) and recurrence-free survival (RFS). Kaplan–Meier estimates were used to compare RFS and OS rates between groups.

Result PA-TACE was not an independent prognostic factor for RFS (entire cohort: hazard ratio [HR] 1.17, 95% confidence interval [CI] 0.92–1.50, $p = 0.206$; matched cohort: HR 1.10, 95% CI 0.79–1.54, $p = 0.560$) or OS (entire cohort: HR 1.15, 95% CI 0.87–1.52, $p = 0.317$; matched cohort: HR 0.96, 95% CI 0.68–1.36, $p = 0.823$). In the matched cohort, independent Predictors of worse OS included tumor diameter ≥ 5 cm, positive microvascular invasion (MVI), Edmondson-Steiner grade III-IV, pathological cirrhosis, and Barcelona Clinic Liver Cancer (BCLC) B/C stage. Predictors of worse RFS included tumor diameter ≥ 5 cm and Edmondson-Steiner grade III-IV. Only in the BCLC B/C stage subgroup, PA-TACE may improve OS compared to non-PA-TACE (HR 0.47, 95% CI 0.26–0.85, $p = 0.011$).

Conclusion PA-TACE may not extend OS or RFS in HCC patients with BCLC 0/A stage, tumor diameter ≥ 5 cm, or MVI. PA-TACE should be administered with caution, even in HCC patients with BCLC B/C stage.

Keywords Hepatocellular carcinoma · Postoperative adjuvant TACE · Overall survival · Recurrence-free survival · Propensity score matching · BCLC stage

Introduction

Hepatocellular carcinoma (HCC) is a highly malignant tumor and ranks as the third leading cause of cancer-related mortality globally, with an annual death toll of 757,948 [1]. Liver resection remains the primary treatment for selected patients with intermediate-stage HCC and has demonstrated effectiveness in this population [2]. Nonetheless, the risk of recurrence post-surgery remains substantial. Transarterial chemoembolization (TACE) was initially established as the standard treatment for unresectable liver cancer [3]. In addition, TACE is frequently employed as a postoperative adjuvant therapy, typically commencing around 4 weeks after surgery. This approach is believed to reduce recurrence risk and extend survival in HCC patients [4–6].

However, the efficacy of postoperative adjuvant transarterial chemoembolization (PA-TACE) has been a subject

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of debate [7]. Emerging evidence suggests that it may not improve recurrence-free survival (RFS) or overall survival (OS) and could potentially be harmful to certain patient subgroups [8]. For instance, Wang et al. reported that PA-TACE did not benefit patients with HCC featuring microvascular invasion (MVI) within the Milan criteria [9]. Risk factors such as tumor diameter exceeding 5 cm, multiple nodules, MVI, macrovascular invasion, tumor thrombus, and poor Edmondson-Steiner grade are associated with a higher recurrence risk [4]. Conversely, substantial evidence indicates that for high-risk populations, PA-TACE can significantly reduce recurrence rates and prolong survival [10–12].

This study aims to assess the efficacy of PA-TACE as a preventative measure for HCC patients without residual tumor, recurrence, or metastasis following liver resection. We applied strict exclusion criteria, mandating that treatments begin within 2 months of R0 liver resection and excluding patients who experience recurrence and undergo treatment within this period. To enhance the reliability of our findings, we employed propensity score matching (PSM) analysis to mitigate patient selection bias. This study identifies suitable and adverse patient populations for PA-TACE.

Methods

Participants and criteria

This retrospective study utilized data from a single medical center, with approval from the Clinical Research Ethics Committee of the Affiliated Tumor Hospital of Guangxi Medical University, following the Declaration of Helsinki and current ethical guidelines.

Between January 2014 and December 2019, we retrospectively enrolled 1035 patients with hepatocellular carcinoma (HCC) who underwent hepatetomy at the Affiliated Tumor Hospital of Guangxi Medical University. Postoperative adjuvant therapy was defined as treatment initiated in the absence of tumor recurrence. Exclusion criteria included: 1) prior treatment for HCC before initial hepatic resection with curative intent; 2) residual tumors confirmed by intraoperative visual inspection and positive resection margins based on histological examination; 3) tumor recurrence indicated by imaging or alpha-fetoprotein (AFP) levels not decreasing to < 400 ng/mL within 2 months post-operation; 4) PA-TACE commenced more than 60 days after surgery; 5) receipt of other postoperative or neoadjuvant therapies. The Edmondson-Steiner grade was judged on the highest grade found in the specimen. The tumor diameter was defined as the maximum diameter of all tumors. The tumor margin was based on imaging characteristics, referring to the visible boundary between the tumor and the surrounding normal liver tissue. We calculated the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Platelet Ratio (NPR), and Systemic Immune-Inflammatory Index (SII) according to the following equations: NLR = neutrophil count/lymphocyte count; PLR = platelet count/lymphocyte count; NPR = neutrophil count/ platelet count; SII = (neutrophil count × platelet count)/lymphocyte count. NLR, PLR, NPR, and SII were categorized into high and low groups based on their respective median cutoff values. A flow chart detailing patient enrollment is shown in Fig. 1.

Postoperative adjuvant TACE

PA-TACE was performed using the Seldinger technique. A vascular catheter was inserted via the femoral artery into the hepatic artery for hepatic angiography. Then preventive chemoembolization was done depending on the patients without tumor stain in the remnant liver. A mixture of chemotherapy agents (oxaliplatin, lobaplatin, pirarubicin) and embolic agents (lipiodol, gelatin sponge) was injected into the residual liver, based on a comprehensive assessment of the patient's body surface area, physical condition, and residual liver volume.

Follow-up

Patients were monitored every 1–2 months for the first 6 months post-discharge, and subsequently every 3–6 months. Routine follow-up included liver function tests, AFP analysis, computed tomography (CT), and magnetic resonance imaging (MRI). Tumor recurrence was defined as new nodules confirmed by ultrasound, enhanced CT, enhanced MRI, and contrast-enhanced ultrasound (CEUS). Recurrence management involves a multidisciplinary approach, including re-hepatectomy, ablation, TACE, radiotherapy, targeted therapy, or conservative treatment. Recurrence-free survival (RFS) was defined as the time from hepatectomy to tumor recurrence or last follow-up, while overall survival (OS) was defined as the time from hepatectomy to death or last follow-up.

Statistical analysis

Propensity score matching (PSM) analysis was used to address inter-group imbalances, employing a 1:1 nearest neighbor matching algorithm with a caliper of 0.02. The balance between groups post-matching was assessed using the standardized mean difference ($p < 0.1$). Continuous variables were analyzed with an independent samples t-test if normally distributed, and reported as mean ± standard deviation (SD). Non-normally distributed continuous variables were analyzed with the Mann–Whitney U test and reported as median (interquartile range, IQR). Categorical variables were

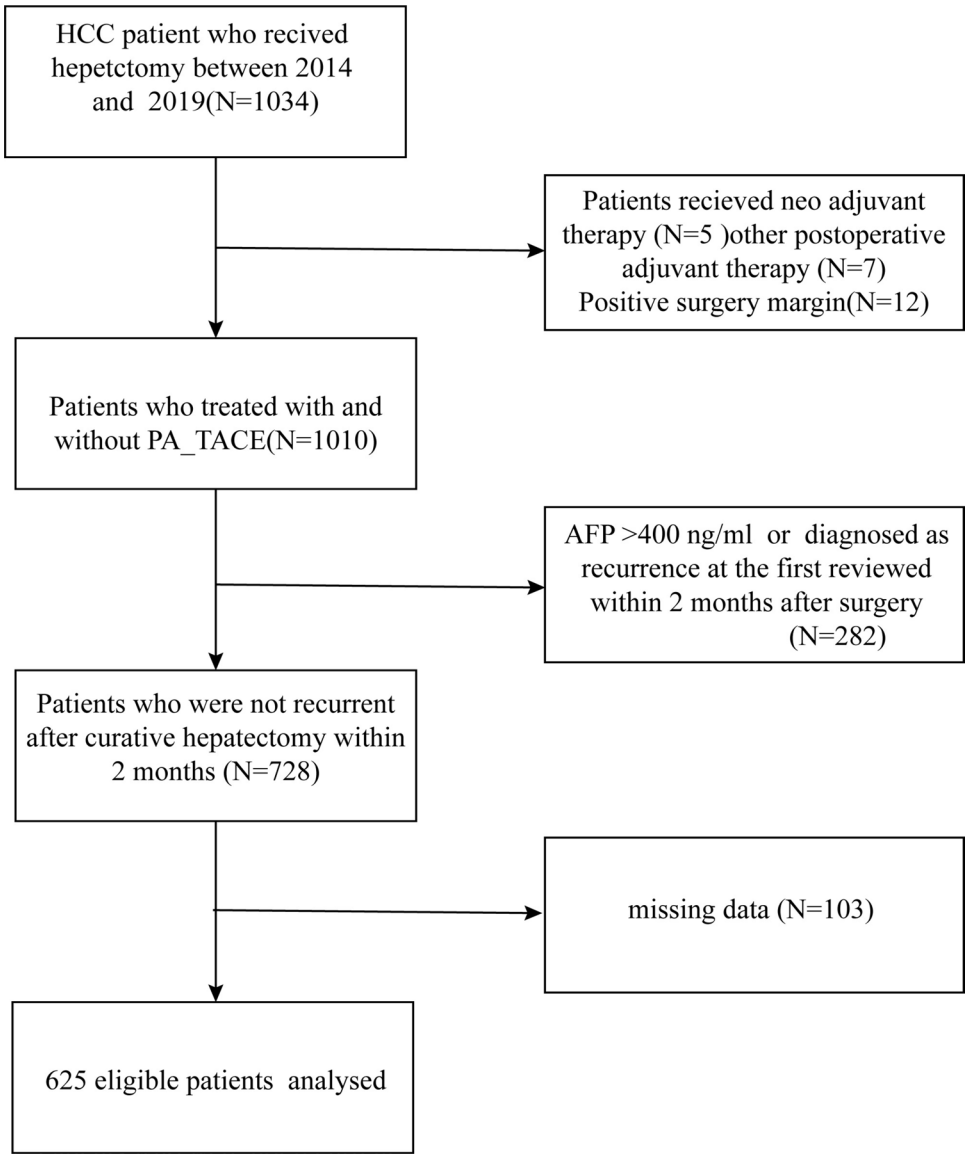

Fig. 1 Flowchart of patient selection

expressed as frequencies and compared using the chi-square test or Fisher's exact test. Univariate and multivariate analyses were conducted using the Cox proportional hazards model to identify independent prognostic factors for RFS and OS. Variables with $P < 0.05$ in univariate analysis were included in multivariate analysis. OS and RFS rates were calculated using the Kaplan–Meier method and estimated by the logarithmic rank test. Statistical analysis was performed using R software (Version 4.2.1; http://www.r-project.org). A two-tailed p-value < 0.05 was considered statistically significant.

Result

Baseline characteristics

Following PSM, a total of 374 patients (187 without PA-TACE and 187 with PA-TACE) were included from an initial cohort of 615 patients (376 without PA-TACE and 249 with PA-TACE). Table 1 presents the clinical characteristics of HCC patients who received PA-TACE

Table 1 Baseline characteristics of hepatocellular carcinoma patients in different treatment groups

Variables	Levels	Before PSM		P	After PSM		P
		Non-PA-TACE ($N=376$)	PA-TACE ($N=249$)		Non-PA-TACE ($N=187$)	PA-TACE ($N=187$)	
Gender	female	68 (18.1%)	32 (12.9%)	0.102	24 (12.8%)	27 (14.4%)	0.763
	male	308 (81.9%)	217 (87.1%)		163 (87.2%)	160 (85.6%)	
Age* (year)	Median (IQR)	51.0 (44.0 to 61.0)	50.0 (41.0 to 57.0)	0.008	50.0 (44.0 to 59.0)	52.0 (43.0 to 58.0)	0.531
DM	No	346 (92%)	230 (92.4%)	0.995	177 (94.7%)	172 (92%)	0.408
	Yes	30 (8%)	19 (7.6%)		10 (5.3%)	15 (8%)	
HBsAg	Negative	68 (18.1%)	40 (16.1%)	0.585	27 (14.4%)	38 (20.3%)	0.172
	Positive	308 (81.9%)	209 (83.9%)		160 (85.6%)	149 (79.7%)	
HBeAg	Negative	305 (81.1%)	215 (86.3%)	0.109	156 (83.4%)	160 (85.6%)	0.668
	Positive	71 (18.9%)	34 (13.7%)		31 (16.6%)	27 (14.4%)	
HBV viral load (IU/mL)	<500	173 (46%)	108 (43.4%)	0.571	86 (46%)	89 (47.6%)	0.836
	≥ 500	203 (54%)	141 (56.6%)		101 (54%)	98 (52.4%)	
HCV	Negative	370 (98.4%)	247 (99.2%)	0.617	187 (100%)	185 (98.9%)	0.478
	Positive	6 (1.6%)	2 (0.8%)		0 (0%)	2 (1.1%)	
Total bilirubin (μmol/L)	<17.1	363 (96.5%)	245 (98.4%)	0.254	185 (98.9%)	183 (97.9%)	0.681
	≥ 17.1	13 (3.5%)	4 (1.6%)		2 (1.1%)	4 (2.1%)	
Albumin (g/L)	<35	355 (94.4%)	242 (97.2%)	0.149	179 (95.7%)	180 (96.3%)	1.000
	≥ 35	21 (5.6%)	7 (2.8%)		8 (4.3%)	7 (3.7%)	
ALBI	≤ -2.60	163 (43.4%)	135 (54.2%)	0.010	84 (44.9%)	95 (50.8%)	0.301
	> -2.60	213 (56.6%)	114 (45.8%)		103 (55.1%)	92 (49.2%)	
AFP (ng/mL)	<400	255 (67.8%)	138 (55.4%)	0.002	119 (63.6%)	116 (62%)	0.831
	≥ 400	121 (32.2%)	111 (44.6%)		68 (36.4%)	71 (38%)	
Splenomegaly	No	208 (55.3%)	134 (53.8%)	0.774	109 (58.3%)	103 (55.1%)	0.602
	Yes	168 (44.7%)	115 (46.2%)		78 (41.7%)	84 (44.9%)	
Ascites	No	323 (85.9%)	227 (91.2%)	0.064	167 (89.3%)	168 (89.8%)	1.000
	Yes	53 (14.1%)	22 (8.8%)		20 (10.7%)	19 (10.2%)	
Fatty liver	No	362 (96.3%)	242 (97.2%)	0.694	183 (97.9%)	180 (96.3%)	0.540
	Yes	14 (3.7%)	7 (2.8%)		4 (2.1%)	7 (3.7%)	
Biliary dilatation	No	228 (60.6%)	153 (61.4%)	0.905	119 (63.6%)	108 (57.8%)	0.290
	Yes	148 (39.4%)	96 (38.6%)		68 (36.4%)	79 (42.2%)	
Tumor number	1	268 (71.3%)	174 (69.9%)	0.775	136 (72.7%)	136 (72.7%)	1.000
	≥ 2	108 (28.7%)	75 (30.1%)		51 (27.3%)	51 (27.3%)	
Tumor diameter (cm)	<5	220 (58.5%)	120 (48.2%)	0.014	94 (50.3%)	95 (50.8%)	1.000
	≥ 5	156 (41.5%)	129 (51.8%)		93 (49.7%)	92 (49.2%)	
Tumor margin	well-defined	229 (60.9%)	153 (61.4%)	0.958	118 (63.1%)	116 (62%)	0.915
	poorly-defined	147 (39.1%)	96 (38.6%)		69 (36.9%)	71 (38%)	
Cirrhosis	No	167 (44.4%)	112 (45%)	0.955	86 (46%)	80 (42.8%)	0.603
	Yes	209 (55.6%)	137 (55%)		101 (54%)	107 (57.2%)	
Child–Pugh grade	A	350 (93.1%)	246 (98.8%)	0.002	180 (96.3%)	185 (98.9%)	0.177
	B	26 (6.9%)	3 (1.2%)		7 (3.7%)	2 (1.1%)	
Direct bilirubin (μmol/L)	<7.5	363 (96.5%)	245 (98.4%)	0.254	185 (98.9%)	183 (97.9%)	0.681
	≥ 7.5	13 (3.5%)	4 (1.6%)		2 (1.1%)	4 (2.1%)	
Vascular invasion	Negative	347 (92.3%)	223 (89.6%)	0.301	165 (88.2%)	171 (91.4%)	0.392
	Positive	29 (7.7%)	26 (10.4%)		22 (11.8%)	16 (8.6%)	
Edmondson-Steiner grade	I-II	187 (49.7%)	105 (42.2%)	0.076	81 (43.3%)	85 (45.5%)	0.755
	III-IV	189 (50.3%)	144 (57.8%)		106 (56.7%)	102 (54.5%)	
MVI	Negative	258 (68.6%)	133 (53.4%)	$<.001$	103 (55.1%)	109 (58.3%)	0.602
	Positive	118 (31.4%)	116 (46.6%)		84 (44.9%)	78 (41.7%)	

Table 1 (continued)

Variables	Levels	Before PSM		P	After PSM		P
		Non-PA-TACE ($N=376$)	PA-TACE ($N=249$)		Non-PA-TACE ($N=187$)	PA-TACE ($N=187$)	
BCLC stage	0/A	302 (80.3%)	173 (69.5%)	0.003	144 (77%)	146 (78.1%)	0.901
	B/C	74 (19.7%)	76 (30.5%)		43 (23%)	41 (21.9%)	
NLR	low	190 (50.5%)	123 (49.4%)	0.845	95 (50.8%)	94 (50.3%)	1.000
	high	186 (49.5%)	126 (50.6%)		92 (49.2%)	93 (49.7%)	
SII	low	198 (52.7%)	115 (46.2%)	0.133	93 (49.7%)	94 (50.3%)	1.000
	high	178 (47.3%)	134 (53.8%)		94 (50.3%)	93 (49.7%)	
PLR	low	189 (50.3%)	124 (49.8%)	0.974	98 (52.4%)	93 (49.7%)	0.679
	high	187 (49.7%)	125 (50.2%)		89 (47.6%)	94 (50.3%)	
NPR	low	186 (49.5%)	127 (51%)	0.769	91 (48.7%)	93 (49.7%)	0.918
	high	190 (50.5%)	122 (49%)		96 (51.3%)	94 (50.3%)	

Data are n (%) and ranges

*Presented as median and ranges

PA-TACE, postoperative adjuvant transarterial chemoembolization; DM, diabetes; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B core antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; MVI, microvascular invasion; BCLC, Barcelona Clinic Liver Cancer; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammatory index; PLR, platelet-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio

versus those who did not. Before PSM, significant differences were observed between the groups in terms of age, albumin-bilirubin (ALBI) score, AFP levels, tumor diameter, Child–Pugh grade, MVI, and Barcelona Clinic Liver Cancer (BCLC) stage ($p<0.05$). Post-PSM, there were no significant differences in clinical characteristics between the two groups.

Predictors of worse OS and RFS

Univariate and multivariate Cox regression analyses were conducted for the entire cohort, with results detailed in Table S1 and Table S2. Multivariate analysis identified tumor diameter > 5 cm (HR: 1.66, 95% CI: 1.23–2.24, $p<0.001$), high NPR (HR: 1.46, 95% CI: 1.10–1.95, $p=0.008$), and BCLC B/C stage (HR: 1.73, 95% CI: 1.23–2.43, $p<0.001$) as independent Predictors of worse OS in HCC patients following hepatectomy. Tumor diameter > 5 cm (HR: 1.35, 95% CI: 1.04–1.75, $p=0.022$) and BCLC B/C stage (HR: 1.51, 95% CI: 1.13–2.01, $p=0.005$) were identified as independent Predictors of worse RFS.

In the matched cohort, univariate and multivariate Cox regression analyses are summarized in Tables 2 and 3. Multivariate analysis revealed tumor diameter > 5 cm (HR: 1.72, 95% CI: 1.18–2.52, $p=0.005$), cirrhosis (HR: 1.50, 95% CI: 1.02–2.20, $p=0.039$), Edmondson-Steiner grade III = IV (HR: 1.54, 95% CI: 1.06–2.23, $p=0.024$), MVI (HR: 1.58, 95% CI: 1.08–2.30, $p=0.018$), and BCLC B/C stage (HR: 1.75, 95% CI: 1.12–2.74, $p=0.015$) as independent risk factors affecting OS after hepatectomy. For RFS, HBV viral load > 500 IU/mL(HR: 1.44, 95% CI: 1.01–2.04, $p=0.042$), tumor diameter > 5 cm (HR: 1.55, 95% CI: 1.10–2.20, $p=0.013$), and Edmondson-Steiner grade III = IV (HR: 1.68, 95% CI: 1.19–2.37, $p=0.003$) were identified as independent risk factors.

PA-TACE was not associated with improved prognosis for RFS or OS in HCC patients following radical surgery. During the follow-up period, there were 256 tumor recurrences and 200 deaths in the entire cohort. In the matched cohort, there were 142 tumor recurrences and 126 deaths. Kaplan–Meier curves demonstrated that RFS and OS in the PA-TACE group were comparable to those in the non-PA-TACE group, with no significant differences observed (all $p>0.05$) (Fig. 2).

Subgroup analysis

Stratified analyses of independent prognostic factors affecting RFS and OS were performed for both the entire and matched cohorts. Before propensity matching, the non-cirrhotic HCC subgroup analysis showed 1-year, 3-year, and 5-year RFS rates of 64.7%, 35.1%, and 28.8%, respectively, in the PA-TACE group, compared with 75.7%, 56.5%, and 46.4% in the non-PA-TACE group. The non-PA-TACE group had significantly better RFS compared to the PA-TACE group in the non-cirrhotic HCC subgroup (HR: 1.570, 95% CI: 1.065–2.314, $p=0.023$) (Fig. 3). In the matched cohort, the BCLC B/C stage subgroup analysis revealed 1-year, 3-year, and 5-year OS rates of 95.1%, 75.6%, and 58.3%, respectively, in the PA-TACE group, versus 67.4%, 41.7%, and 35.3% in the non-PA-TACE group. The PA-TACE group had significantly better OS in the BCLC B/C stage subgroup

Table 2 Univariable and multivariable analysis of prognostic factors for overall survival in HCC patients following hepatectomy after PSM

Variables	Levels	stats	HR (univariable)	HR (multivariable)
PA-TACE	Non PA-TACE	187 (50.0%)		
	PA-TACE	187 (50.0%)	0.96 (0.68–1.36, $p=0.823$)	
Gender	female	51 (13.6%)		
	male	323 (86.4%)	1.12 (0.67–1.86, $p=0.672$)	
Age (year)	<60	291 (77.8%)		
	≥ 60	83 (22.2%)	1.36 (0.92–2.03, $p=0.126$)	
DM	No	349 (93.3%)		
	Yes	25 (6.7%)	1.14 (0.58–2.24, $p=0.711$)	
HBsAg	Negative	65 (17.4%)		
	Positive	309 (82.6%)	0.83 (0.53–1.28, $p=0.395$)	
HBeAg	Negative	316 (84.5%)		
	Positive	58 (15.5%)	1.39 (0.89–2.17, $p=0.145$)	
HBV viral load (IU/mL)	<500	175 (46.8%)		
	≥ 500	199 (53.2%)	1.33 (0.93–1.90, $p=0.115$)	
HCV	Negative	372 (99.5%)		
	Positive	2 (0.5%)		
Total bilirubin (μmol/L)	<17.1	368 (98.4%)		
	≥ 17.1	6 (1.6%)	0.88 (0.22–3.56, $p=0.859$)	
Albumin (g/L)	<35	359 (96.0%)		
	≥ 35	15 (4.0%)	1.55 (0.72–3.32, $p=0.260$)	
ALBI	≤ -2.60	179 (47.9%)		
	> -2.60	195 (52.1%)	1.13 (0.80–1.61, $p=0.485$)	
AFP (ng/mL)	<400	235 (62.8%)		
	≥ 400	139 (37.2%)	0.70 (0.48–1.03, $p=0.068$)	
Splenomegaly	No	212 (56.7%)		
	Yes	162 (43.3%)	1.30 (0.92–1.85, $p=0.139$)	
Ascites	No	335 (89.6%)		
	Yes	39 (10.4%)	1.36 (0.79–2.33, $p=0.265$)	
Fatty liver	No	363 (97.1%)		
	Yes	11 (2.9%)		
Biliary dilatation	No	227 (60.7%)		
	Yes	147 (39.3%)	1.13 (0.79–1.61, $p=0.501$)	
Tumor number	1	272 (72.7%)		
	≥ 2	102 (27.3%)	1.57 (1.08–2.28, $p=0.018$)	1.14 (0.74–1.75, $p=0.559$)
Tumor diameter (cm)	<5	189 (50.5%)		
	≥ 5	185 (49.5%)	1.86 (1.30–2.66, $p<.001$)	1.72 (1.18–2.52, $p=0.005$)
Tumor margin	well-defined	234 (62.6%)		
	poorly-defined	140 (37.4%)	1.27 (0.89–1.81, $p=0.179$)	
Cirrhosis	No	166 (44.4%)		
	Yes	208 (55.6%)	1.61 (1.12–2.33, $p=0.011$)	1.50 (1.02–2.20, $p=0.039$)
Direct bilirubin (μmol/L)	<7.5	368 (98.4%)		
	≥ 7.5	6 (1.6%)	0.88 (0.22–3.56, $p=0.859$)	
Vascular invasion	Negative	336 (89.8%)		
	Positive	38 (10.2%)	1.88 (1.15–3.06, $p=0.011$)	1.09 (0.64–1.84, $p=0.755$)
Edmondson-Steiner grade	I-II	166 (44.4%)		
	III-IV	208 (55.6%)	1.61 (1.11–2.32, $p=0.011$)	1.54 (1.06–2.23, $p=0.024$)
MVI	Negative	212 (56.7%)		
	Positive	162 (43.3%)	1.93 (1.36–2.75, $p<0.001$)	1.58 (1.08–2.30, $p=0.018$)
BCLC stage	0/A	290 (77.5%)		

Table 2 (continued)

Variables	Levels	stats	HR (univariable)	HR (multivariable)
	B/C	84 (22.5%)	2.45 (1.70–3.52, $p<0.001$)	1.75 (1.12–2.74, $p=0.015$)
NLR	low	189 (50.5%)		
	high	185 (49.5%)	1.00 (0.70–1.41, $p=0.981$)	
SII	low	187 (50.0%)		
	high	187 (50.0%)	0.88 (0.62–1.24, $p=0.455$)	
PLR	low	191 (51.1%)		
	high	183 (48.9%)	0.86 (0.61–1.23, $p=0.416$)	
NPR	low	184 (49.2%)		
	high	190 (50.8%)	1.40 (0.98–1.99, $p=0.061$)	

Data are n (%) and ranges

PA-TACE, postoperative adjuvant transarterial chemoembolization; DM, diabetes; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B core antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; MVI, microvascular invasion; BCLC, Barcelona Clinic Liver Cancer; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammatory index; PLR, platelet-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio

(HR: 0.466, 95% CI: 0.256–0.848, $p=0.01$) (Fig. 4). No significant differences were observed in other subgroups for RFS and OS, regardless of whether the cohort was before or after matching (Figure S1-S4).

Discussion

While variability in the response to TACE is evident, even among high-risk recurrence populations, this variability may stem from biases in population selection. The Chinese liver cancer guidelines advocate for adjuvant TACE in postoperative HCC patients at high risk of recurrence, excluding those who experience recurrence within two months post-surgery [4]. To ensure the accuracy of our analysis and validate the benefits of PA-TACE, we adhered strictly to the Chinese Guidelines for the Diagnosis and Treatment of Primary Liver Cancer [4]. Our findings indicate that PA-TACE does not serve as a prognostic factor for RFS and OS in HCC patients after radical surgery, except for an extension of OS in patients with BCLC B/C stage HCC in the matched cohort. Furthermore, TACE may be detrimental to HCC patients without cirrhosis before PSM.

HCC, due to the liver's rich blood supply, often presents early as large, multifocal tumors, vascular invasion, and tumor thrombus. MVI correlates with larger tumor sizes (≥ 5 cm) and multifocality, leading to intrahepatic metastases and early recurrence [13–15]. Multiple nodules are associated with multicentric tumors or undetectable micrometastases [16]. Postoperative pathology frequently reveals microvascular invasion, satellite nodules, and subfocal lesions, indicating that macroscopic tumor resection may not eliminate undetected micrometastases distributed through the vascular system, potentially resulting in early postoperative recurrence [17]. Early recurrence is closely linked with poor prognosis in HCC patients. Pathological cirrhosis often involves liver inflammation, fibrosis, and cell proliferation, altering the hepatic microenvironment and supporting tumor regeneration [18]. Zhou et al. identified Edmondson-Steiner grade as an independent predictor of overall and disease-free survival [19]. Chronic hepatitis B virus infection can cause persistent hepatic inflammation and cirrhosis, contributing to HCC and its recurrence after therapy [20]. Positive HBeAg is associated with higher early recurrence risk and poorer prognosis post-curative resection of small HCC [21]. Poor liver function, high HBV replication, and an immunosuppressive environment are closely linked to recurrence.

PA-TACE does not appear to improve outcomes and may even promote postoperative recurrence in low-risk HCC patients [8, 22–24]. Similarly, in our cohort of HCC patients with BCLC 0/A stage, MVI negative, tumor diameter <5 cm, and Edmondson-Steiner grade I-II, PA-TACE did not enhance RFS or OS. Even in high-risk populations, PA-TACE did not demonstrate benefits [9]. PA-TACE may exacerbate hepatic inflammation, immune suppression, and virus reactivation, and deteriorate liver function [25–28]. The potential adverse effects of TACE include damage to the remnant liver and impaired liver function, which may negate any potential improvement in RFS or OS if the initial resection was truly curative. The perceived benefits of PA-TACE in high-risk recurrence patients may stem from the visible iodized oil deposition following hepatic artery embolization, facilitating early recurrence diagnosis and possibly leading to improved liver function and more aggressive therapy upon early recurrence. However, deterioration of residual liver function may diminish or negate the benefits in patients with lower risks of intrahepatic metastases or residual tumors. PA-TACE may reduce early recurrence and improve survival due to therapeutic actions on residual tumors [24]. Some researchers argue that TACE may not

Table 3 Univariable and multivariable analysis of prognostic factors for recurrence-free survival in HCC patients following hepatectomy after PSM

Variables	Levels	stats	HR (univariable)	HR (multivariable)
PA-TACE	Non PA-TACE	187 (50.0%)		
	PA-TACE	187 (50.0%)	1.10 (0.79–1.54, $p=0.560$)	
Gender	female	51 (13.6%)		
	male	323 (86.4%)	0.95 (0.59–1.50, $p=0.812$)	
Age (year)	<60	291 (77.8%)		
	≥ 60	83 (22.2%)	0.94 (0.63–1.41, $p=0.775$)	
DM	No	349 (93.3%)		
	Yes	25 (6.7%)	1.33 (0.72–2.47, $p=0.361$)	
HBsAg	Negative	65 (17.4%)		
	Positive	309 (82.6%)	1.43 (0.89–2.29, $p=0.141$)	
HBeAg	Negative	316 (84.5%)		
	Positive	58 (15.5%)	1.11 (0.73–1.70, $p=0.628$)	
HBV viral load (IU/mL)	<500	175 (46.8%)		
	≥ 500	199 (53.2%)	1.59 (1.12–2.23, $p=0.009$)	1.44 (1.01–2.04, $p=0.042$)
HCV	Negative	372 (99.5%)		
	Positive	2 (0.5%)		
Total bilirubin (μmol/L)	<17.1	368 (98.4%)		
	≥ 17.1	6 (1.6%)	0.84 (0.12–5.99, $p=0.859$)	
Albumin (g/L)	<35	359 (96.0%)		
	≥ 35	15 (4.0%)	0.41 (0.10–1.65, $p=0.207$)	
ALBI	≤ -2.60	179 (47.9%)		
	> -2.60	195 (52.1%)	0.79 (0.57–1.09, $p=0.155$)	
AFP (ng/mL)	<400	235 (62.8%)		
	≥ 400	139 (37.2%)	0.93 (0.66–1.30, $p=0.676$)	
Splenomegaly	No	212 (56.7%)		
	Yes	162 (43.3%)	1.03 (0.74–1.43, $p=0.883$)	
Ascites	No	335 (89.6%)		
	Yes	39 (10.4%)	1.18 (0.69–2.02, $p=0.540$)	
Fatty liver	No	363 (97.1%)		
	Yes	11 (2.9%)	0.18 (0.03–1.29, $p=0.087$)	
Biliary dilatation	No	227 (60.7%)		
	Yes	147 (39.3%)	0.89 (0.63–1.25, $p=0.490$)	
Tumor number	1	272 (72.7%)		
	≥ 2	102 (27.3%)	1.07 (0.75–1.51, $p=0.709$)	
Tumor diameter (cm)	<5	189 (50.5%)		
	≥ 5	185 (49.5%)	1.67 (1.20–2.34, $p=0.003$)	1.55 (1.10–2.20, $p=0.013$)
Tumor margin	well-defined	234 (62.6%)		
	poorly-defined	140 (37.4%)	1.42 (1.01–1.98, $p=0.041$)	1.29 (0.92–1.81, $p=0.133$)
Cirrhosis	No	166 (44.4%)		
	Yes	208 (55.6%)	1.26 (0.90–1.76, $p=0.182$)	
Direct bilirubin (μmol/L)	<7.5	368 (98.4%)		
	≥ 7.5	6 (1.6%)	0.84 (0.12–5.99, $p=0.859$)	
Vascular invasion	Negative	336 (89.8%)		
	Positive	38 (10.2%)	1.21 (0.73–2.01, $p=0.455$)	
Edmondson-Steiner grade	I-II	166 (44.4%)		
	III-IV	208 (55.6%)	1.64 (1.16–2.31, $p=0.005$)	1.68 (1.19–2.37, $p=0.003$)
MVI	Negative	212 (56.7%)		

Table 3 (continued)

Variables	Levels	stats	HR (univariable)	HR (multivariable)
	Positive	162 (43.3%)	1.19 (0.85–1.65, $p=0.309$)	
BCLC stage	0/A	290 (77.5%)		
	B/C	84 (22.5%)	1.71 (1.19–2.44, $p=0.003$)	1.43 (0.98–2.07, $p=0.063$)
NLR	low	189 (50.5%)		
	high	185 (49.5%)	1.02 (0.74–1.42, $p=0.898$)	
SII	low	187 (50.0%)		
	high	187 (50.0%)	1.07 (0.77–1.49, $p=0.687$)	
PLR	low	191 (51.1%)		
	high	183 (48.9%)	0.92 (0.66–1.28, $p=0.618$)	
NPR	low	184 (49.2%)		
	high	190 (50.8%)	1.11 (0.80–1.55, $p=0.524$)	

Data are n (%) and ranges

PA-TACE, postoperative adjuvant transarterial chemoembolization; DM, diabetes; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B core antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; MVI, microvascular invasion; BCLC, Barcelona Clinic Liver Cancer; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammatory index; PLR, platelet-to-lymphocyte ratio; NPR, neutrophil-to-platelet ratio

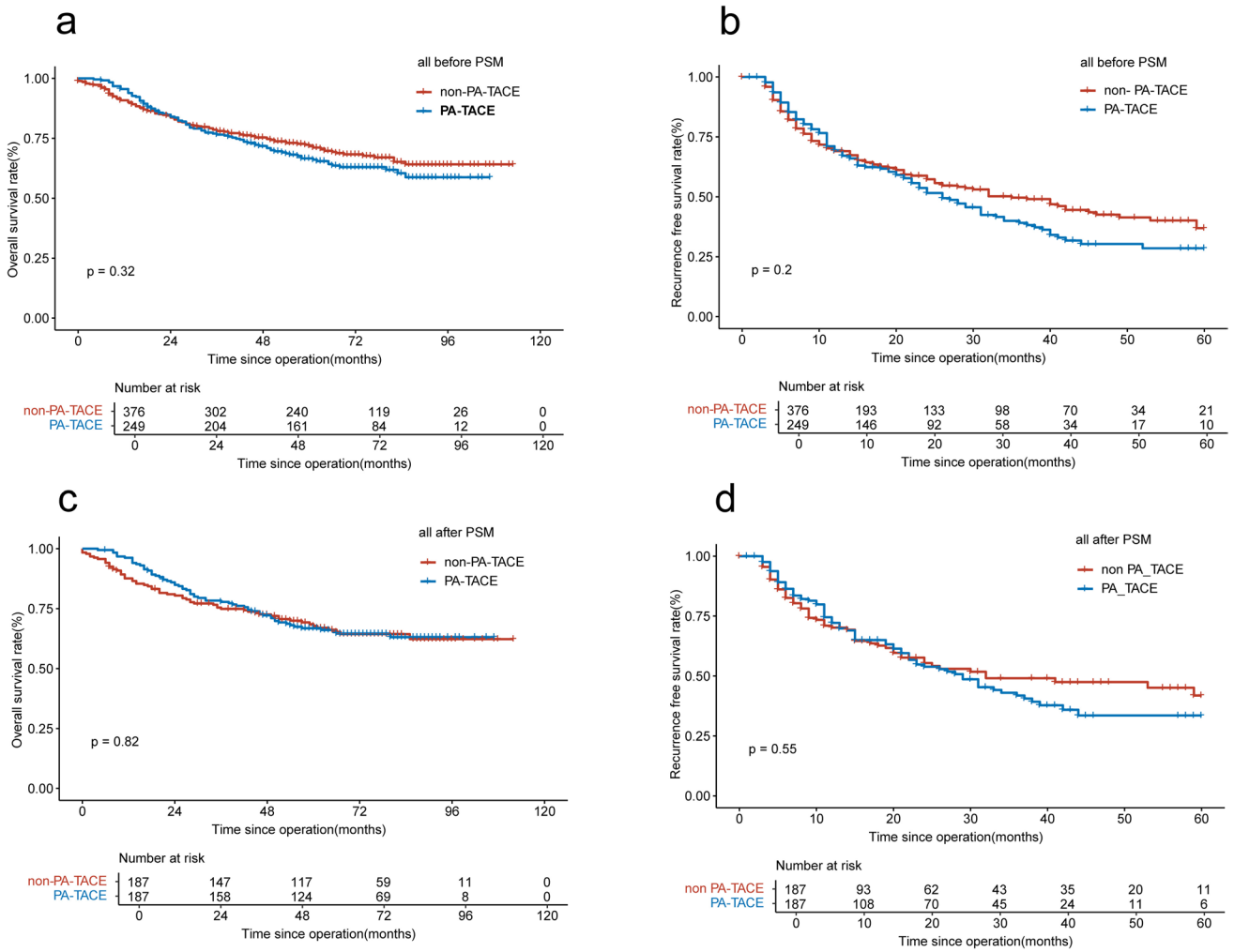

Fig. 2 Kaplan–Meier analysis of OS and RFS in the whole cohort (**a**, **b**), Kaplan–Meier analysis of OS and RFS in the matched cohort (**c**, **d**). Abbreviation: PA-TACE, postoperative adjuvant transarterial chemoembolization

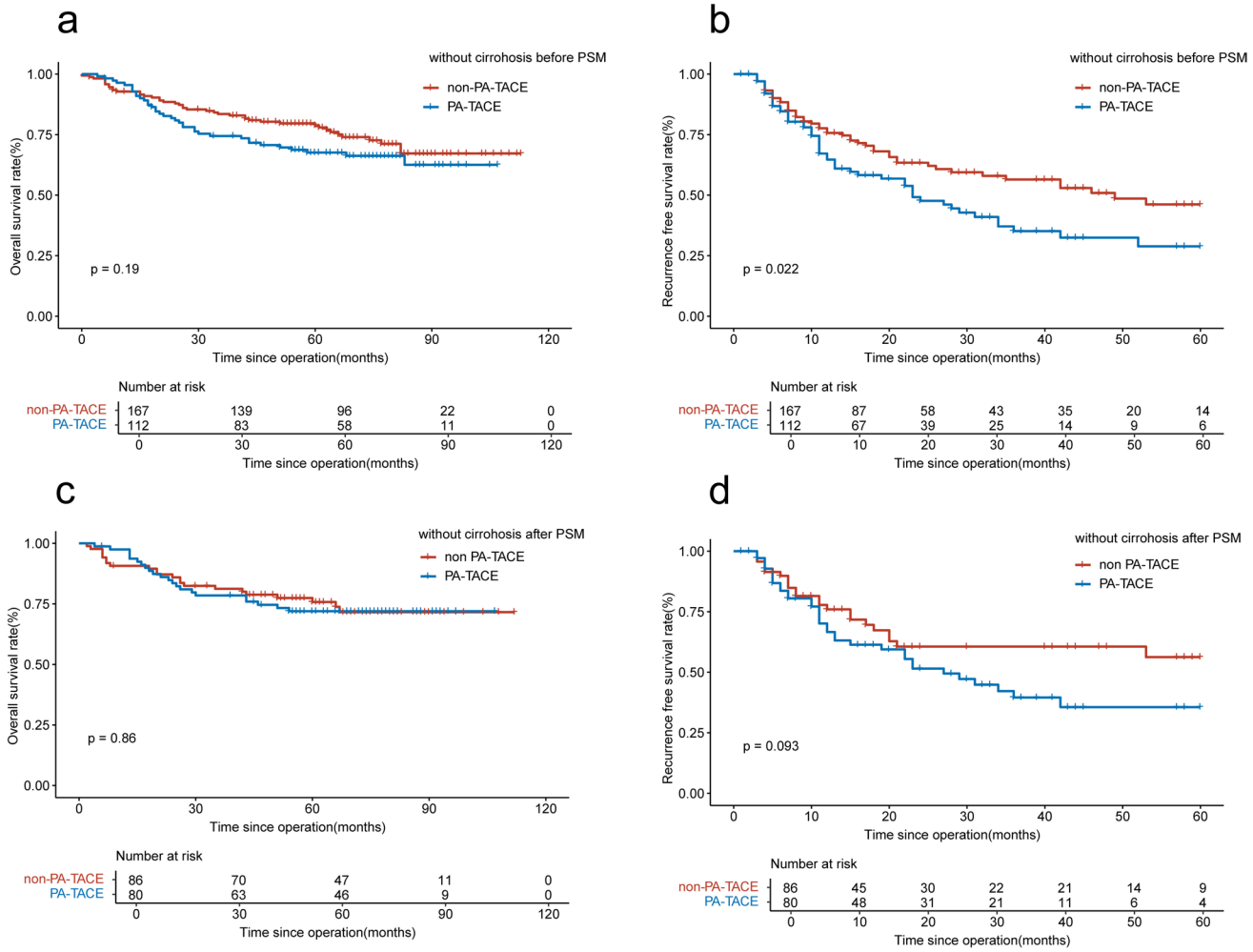

Fig. 3 Kaplan–Meier analysis of OS and RFS in the non-cirrhotic group for the whole cohort (**a**, **b**), Kaplan–Meier analysis of OS and RFS in the non-cirrhotic group for the matched cohort (**c**, **d**). Abbreviation: PA-TACE, postoperative adjuvant transarterial chemoembolization

eradicate residual tumor cells and could potentially facilitate their invasion, accelerating intrahepatic and extrahepatic metastases. Lai et al. found that PA-TACE was associated with extrahepatic metastases and increased recurrence [29]. Our study showed that PA-TACE did not improve overall survival or recurrence-free survival, even in high-risk populations characterized by tumor diameter ≥ 5 cm, MVI positive, and Edmondson-Steiner grade III-IV. Wei et al. observed no beneficial effect of PA-TACE in single, larger tumors [30]. A meta-analysis suggested that patients with multiple HCC and microvascular invasion would not benefit from PA-TACE [7]. Wang et al. demonstrated that less well-differentiated HCC patients did not benefit from PA-TACE [31]. Our study design excluded patients with recurrence within 2 months postoperatively, focusing on those undergoing curative liver resection and retaining a cohort with lower invasiveness and less residual tumor. We hypothesize that high-risk patients with post-curative liver resection may not benefit from PA-TACE, although this remains challenging to confirm. Subgroup analysis of BCLC B/C stage patients indicated that PA-TACE may extend OS. BCLC B/C stage patients often present with advanced tumor characteristics such as MVI, macrovascular invasion, tumor thrombus, distant metastases, and multifocality. Xiang et al. reported that PA-TACE could be beneficial for intermediate-stage HCC patients with microvascular invasion [32]. Our study suggests that PA-TACE may shorten RFS in HCC patients without cirrhosis, possibly due to retrospective case–control study limitations, selection bias, and other confounding factors. Significant differences in clinical baseline data between groups, such as liver function and tumor burden, were addressed through PSM, revealing no statistical differences. Wei et al. found similar results in their randomized study [30].

To minimize the impact of adjuvant TACE on remaining tumors, we excluded patients with severe conditions and those

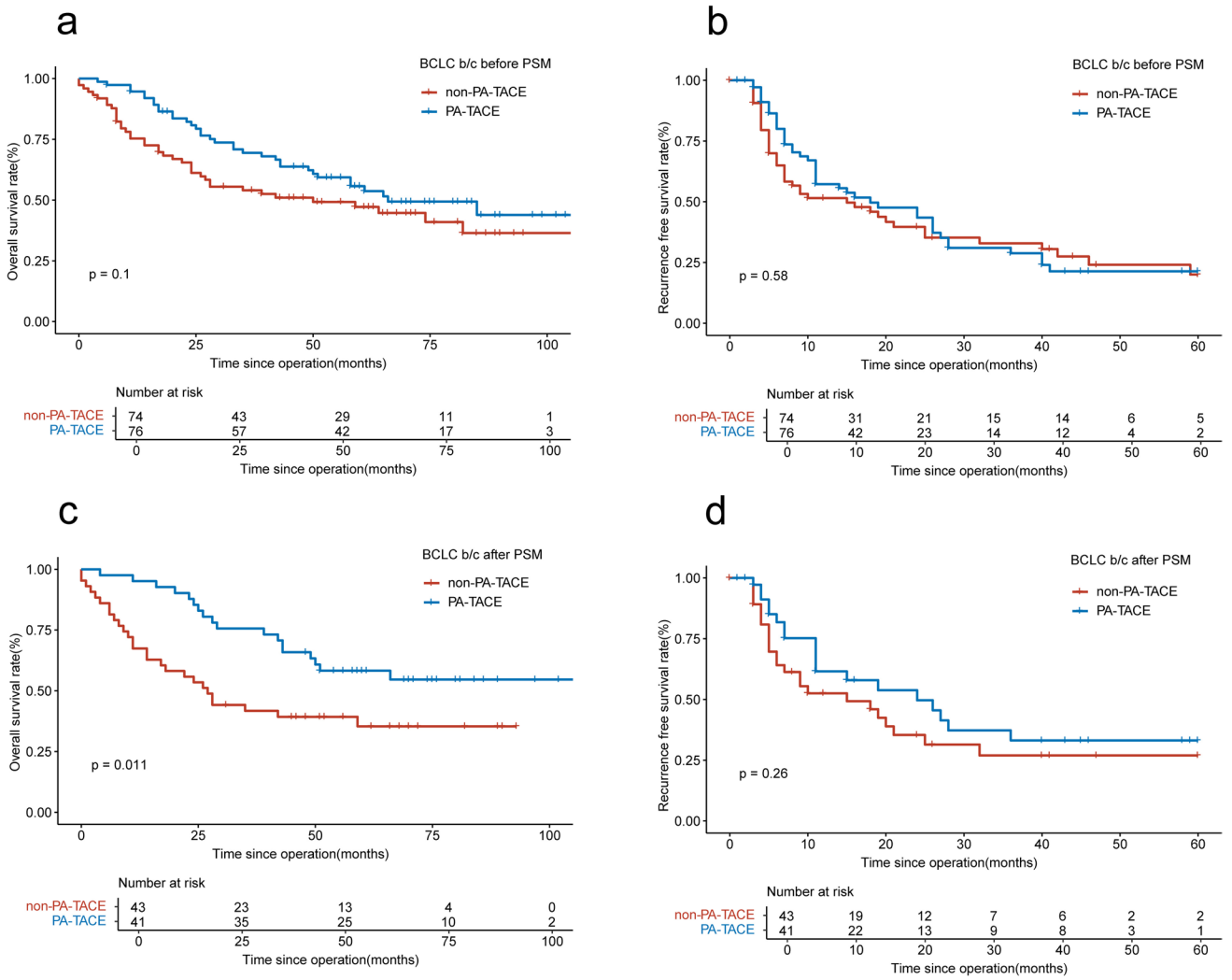

Fig. 4 Kaplan–Meier analysis of OS and RFS in BCLC B/C stage group for the whole cohort (**a**, **b**), Kaplan–Meier analysis of OS and RFS in BCLC B/C stage group for the matched cohort (**c**, **d**). Abbreviation: PA-TACE, postoperative adjuvant transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer

who recurred within two months of liver resection. PA-TACE did not improve RFS or OS in HCC patients, except for those with BCLC B/C stage. Our study has limitations. First, as a single-center cohort study, it is challenging to eliminate all confounding biases despite PSM, Adjuvant TACE after hepatectomy was typically determined based on a comprehensive assessment by the surgeon, considering both intraoperative and postoperative evaluations. Due to selection bias, patients receiving adjuvant TACE may have a higher risk of recurrence compared to those who do not. As a result, even with adjuvant TACE, their outcomes may not necessarily be superior to those of patients who did not undergo the procedure. Second, A potential limitation of this study is the relatively small number of patients with BCLC B/C stage included in the subgroup analysis. This may limit the statistical power and the generalizability of the findings for this subgroup. Third, Current medical technology has limitations in detecting tumor lesions. As a result, some HCC patients with residual tumors may be misclassified as having undergone curative resection, which could impact the assessment of TACE's effectiveness on the prognosis of patients after curative hepatectomy. Additionally, the effect of the number of TACE sessions on treatment outcomes was not explored in depth. Further multicenter prospective studies are needed to provide higher-quality evidence to clarify the benefits of PA-TACE in high-risk recurrence patients.

Conclusion

PA-TACE may not extend OS or RFS in HCC patients with BCLC 0/A stage, tumor diameter ≥ 5 cm, or MVI. PA-TACE should be administered with caution, even in HCC patients with BCLC B/C stage.

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Data availability Data is provided within the manuscript or supplementary information files.

Declarations

Conflict of interest The authors declare no competing interests.

Disclosure The authors report no conflicts of interest in this work.

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