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Adjuvant PD-1 inhibitors improve recurrence and survival outcomes in high-risk hepatocellular carcinoma patients after curative hepatectomy

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Abstract

Background Hepatocellular carcinoma (HCC) is the most prevalent malignancy in China, with liver resection recognized as the primary curative intervention. However, HCC patients face an elevated risk of recurrence, thereby significantly impacting prognosis.

Purpose This study aimed to assess the impact of adjuvant programmed cell death protein-1 (PD-1) inhibitors on survival outcomes in patients with HCC who are at high risk for postoperative recurrence following curative hepatectomy.

Materials and methods Among the 199 study participants, 77 received adjuvant PD-1 inhibitors. Propensity score matching (PSM) was used to balance baseline differences between patients who received adjuvant PD-1 inhibitors and those who did not. Assessment of overall survival (OS) and recurrence-free survival (RFS) was conducted using Kaplan–Meier curves, while Cox regression analysis was employed to identify prognostic factors influencing survival.

Results After PSM, the 1-year and 2-year RFS were 87.1% and 74.2% in the PD-1 inhibitors group and 44.6% and 37.8% in non-PD-1 inhibitors group ($p < 0.001$). The 1-year and 2-year OS were 98.5% and 95.7% in the PD-1 inhibitors group compared with 90.7% and 77.0% in non-PD-1 inhibitors group ($p = 0.004$). Multivariable analyses demonstrated that the use of adjuvant PD-1 inhibitors was significantly associated with improved RFS and OS. Subgroup analysis indicated that adjuvant PD-1 inhibitors group achieved longer RFS than the non-PD-1 inhibitors group in patients without adjuvant transarterial chemoembolization (TACE).

Conclusion The administration of adjuvant PD-1 inhibitors may effectively reduce the risk of tumor recurrence and improve survival in HCC patients with high risk of recurrence after curative hepatectomy.

Keywords Hepatocellular carcinoma, Curative hepatectomy, Programmed cell death protein-1 inhibitors

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Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors in China, with the second-highest mortality rate among malignancies [1]. Currently, liver resection remains the foremost approach for achieving radical treatment and long-term survival in HCC patients. However, the 5-year recurrence rates of HCC after curative hepatectomy remained high, ranging from 50 to 70% [2]. The recurrence of HCC significantly impacts prognosis of patients and is closely linked to tumor characteristics such as vascular invasion, size, multiplicity and satellite nodules [3–5]. Therefore, the urgent demand for efficacious adjuvant therapies to improve prognosis of HCC patients, is underscored. Historically, a spectrum of postoperative adjuvant strategies, including antiviral treatment [6], transarterial chemoembolization (TACE) [7], traditional Chinese medicine [8] and radiotherapy [9], have been deployed in an attempt to curtail tumor relapse and enhance survival rates. However, the efficacy of these treatments remains controversial, and no consensus on a standardized regimen has emerged.

Recently, programmed cell death protein-1 (PD-1) inhibitors have not only made great achievements in the combinational treatment of advanced HCC [10–14], but also demonstrate promising potential in adjuvant therapy post-hepatectomy [15, 16]. By modulating the immunological microenvironment and keeping T cells active, PD-1 inhibitors can improve T cells' capacity to identify and eliminate tumor cells that may have remained [17, 18]. In addition, PD-1 inhibitors have a long-lasting effect, may enhance the immune system's capacity for immunosurveillance [19, 20]. Chen et al. reported that adjuvant PD-1 inhibitors can effectively improve the survival outcomes of HCC patients with high relapse risks after hepatectomy [21]. A multicenter real word study demonstrated that postoperative adjuvant therapy with camrelizumab in combination with apatinib significantly enhanced recurrence-free survival (RFS) benefits in patients with HCC with microvascular invasion (MVI) [22].

In this study, we aim to explore the effectiveness of adjuvant PD-1 inhibitors in HCC patients with high risk of recurrence following curative hepatectomy and contribute valuable insights to postoperative adjuvant treatment strategies of HCC.

Materials and methods

Patients

We conducted a retrospective analysis encompassing all patients with high-risk factors who underwent curative hepatectomy at our institution from April 2020 to December 2023. The inclusion criteria encompassed: (1) age ranging from 18 to 80 years; (2) newly diagnosed and histologically confirmed HCC; (3) Child–Pugh grade A; (4) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; (5) curative hepatectomy with negative surgical margins; (6) presence of one or more high-risk factors for recurrence: vascular invasion (including microvascular invasion or macrovascular invasion), tumor size > 5 cm, multiple tumors, satellite nodules and capsular invasion. Exclusion criteria comprised: (1) history of other malignancies; (2) Child–Pugh grade B or C; (3) post-hepatectomy liver failure; (4) severe dysfunction in other organs; (5) loss to follow-up.

Treatment

Patients underwent a preoperative assessment that included the indocyanine green retention rate at 15 min and the estimation of the future liver remnant volume, all performed by skilled hepatobiliary surgeons. Curative hepatectomy was defined by the attainment of negative surgical margins or by the absence of detectable residual tumors via computed tomography (CT) or magnetic resonance imaging (MRI). Adjuvant PD-1 inhibitors or TACE were recommended after hepatectomy if patients had one or more high-risk factors of recurrence.

The initiation of adjuvant PD-1 inhibitors was scheduled within 4 weeks following curative hepatectomy. PD-1 inhibitors (pembrolizumab 200 mg or tislelizumab 200 mg) were intravenously administered over 60 min every 3 weeks until recurrence of tumor or until intolerable adverse effects were observed, as per the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5.0). The choice of specific PD-1 inhibitors depends on patients' wishes after a discussion with their attending physicians based on the guideline and expert consensus [23, 24]. All patients with viral infection received antiviral treatment. Some patients received one cycle of adjuvant TACE approximately one month following curative hepatectomy; emulsions (~ 5–10 mg) of lipiodol and lobaplatin (at a volume ratio of 1:1) were utilized for chemoembolization.

Follow-up

The primary study endpoint was RFS, with secondary endpoints being overall survival (OS) and the safety of adjuvant treatment. RFS was defined as the time elapsed from the hepatectomy procedure to the detection of tumor recurrence or death. OS was measured from the time of hepatectomy to the time of death. Post-hepatectomy, patients were subjected to a comprehensive re-evaluation every two months, including assessments of alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) levels, liver and kidney function tests, and the liver ultrasound. In cases where tumor

recurrence was suspected, a full examination using CT or MRI was conducted. The study was last followed up on July 1, 2024.

Statistical analyses

The statistical analyses were conducted utilizing SPSS 26.0 and R software version 3.5.2. Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile ranges (IQR). To reduce the influence of confounders, we performed 1:1 propensity score matching (PSM) with a caliper width of 0.25. Comparisons between groups for continuous variables were made using the independent samples t-test, while categorical variables were analyzed using the Chi-square (χ^2) test or Fisher's exact test when appropriate. Survival curves were generated through Kaplan–Meier analysis, with the log-rank test used to compare survival differences. Cox proportional hazards models were applied for univariate and multivariate analyses. Variables significant at $p < 0.05$ in the univariate analysis were included in the multivariate analysis. A p-value of less than 0.05 was considered to indicate statistical significance, denoting the reliability and relevance of the findings.

Results

Characteristics of patients

A total of 431 HCC patients who underwent hepatectomy from April 2020 to December 2023 were initially identified. Following the rigorous screening, 199 patients were included in the final analysis—77 who received adjuvant PD-1 inhibitors and 122 who did not (Fig. 1). The majority of the study population were male (85.93%), and a significant proportion had a history of hepatitis virus infection (87.44%) and cirrhosis (55.78%). Regarding tumor characteristics, 77.89% had a single tumor, and over 50% had a tumor size greater than 5 cm. Detailed patient characteristics before and after PSM are presented in Table 1. Prior to PSM, patients with larger tumor sizes (> 5 cm) were more frequently observed in the PD-1 inhibitors group compared to the non-PD-1 inhibitors group (68.83% vs. 52.46%, $p = 0.022$). Following a 1:1 PSM, baseline characteristics between the two groups were well-matched.

Survival analysis

The median follow-up duration for the 199 patients was 36.0 months (IQR: 32.6–39.4), during which 99 patients experienced recurrence (49.7%) and 37 died (18.6%). The median follow-up was 28.0 months (IQR: 23.5–32.5) for

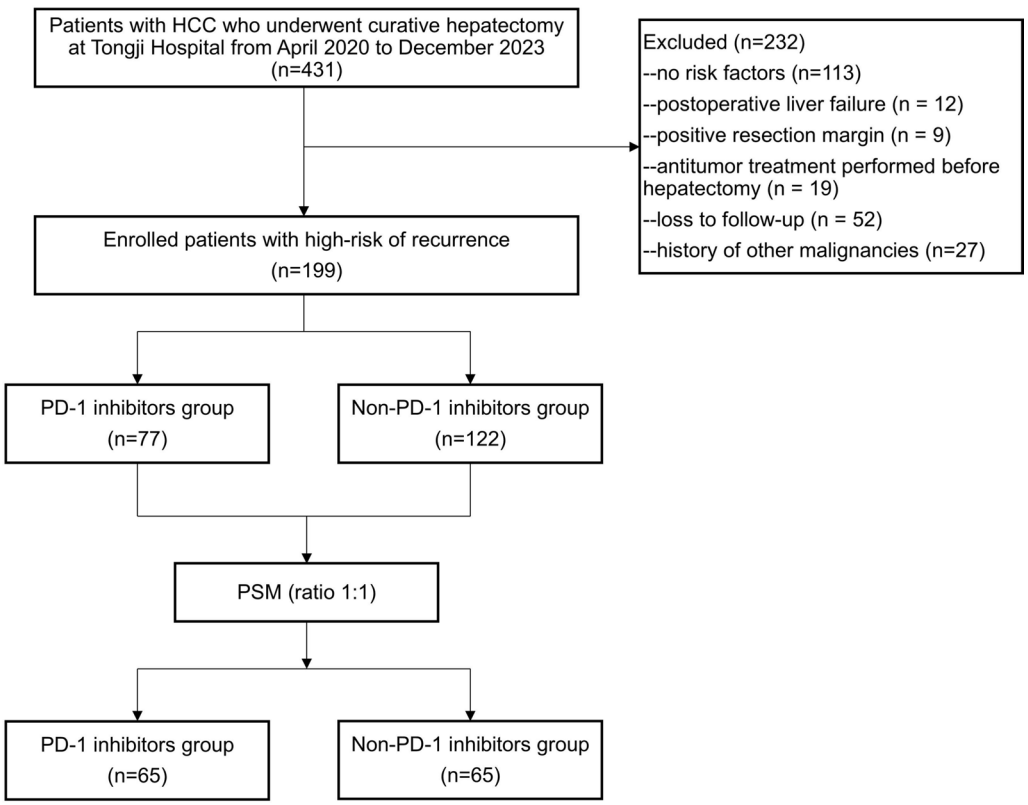

Fig. 1 Flowchart of patient selection

Table 1 Baseline characteristics of the patients

Variable	Before PSM			After PSM		
	No-PD-1 (*n* = 122)	PD-1 (*n* = 77)	*p*	Non-PD-1 (*n* = 65)	PD-1 (*n* = 65)	*p*
Age, mean ± SD	55.86 ± 12.11	54.75 ± 9.53	0.474	55.78 ± 12.57	55.48 ± 9.02	0.873
Sex, *n* (%)			0.443			0.571
Male	103 (84.43)	68 (88.31)		59 (90.77)	57 (87.69)	
Female	19 (15.57)	9 (11.69)		6 (9.23)	8 (12.31)	
WBC, mean ± SD	5.82 ± 2.53	5.60 ± 1.54	0.448	5.80 ± 1.95	5.59 ± 1.62	0.510
PLT, mean ± SD	168.19 ± 73.38	179.32 ± 76.93	0.307	178.66 ± 73.26	175.40 ± 71.15	0.797
Hemoglobin, mean ± SD	134.11 ± 19.04	139.19 ± 18.57	0.065	138.83 ± 14.01	138.15 ± 19.59	0.821
ALT, mean ± SD	28.61 ± 19.09	31.52 ± 35.52	0.455	30.37 ± 20.77	26.83 ± 15.45	0.272
ast, mean ± sd	33.55 ± 17.34	29.81 ± 12.52	0.102	31.66 ± 13.65	29.52 ± 12.48	0.353
ALBI grade, *n* (%)			0.313			0.706
Grade 1	22 (18.03)	12 (15.58)		9 (13.85)	11 (16.92)	
Grade 2	93 (76.23)	56 (72.73)		51 (78.46)	47 (72.31)	
Grade 3	7 (5.74)	9 (11.69)		5 (7.69)	7 (10.77)	
AFP, *n* (%)			0.721			0.848
< 400 ng/ml	81 (66.39)	53 (68.83)		45 (69.23)	46 (70.77)	
≥ 400 ng/mL	41 (33.61)	24 (31.17)		20 (30.77)	19 (29.23)	
DCP, *n* (%)			0.815			0.553
< 40 mAU/mL	33 (27.05)	22 (28.57)		16 (24.62)	19 (29.23)	
≥ 400 mAU/mL	89 (72.95)	55 (71.43)		49 (75.38)	46 (70.77)	
Viral infection, *n* (%)			0.707			0.456
HBV	104 (85.25)	68 (88.31)		56 (86.15)	57 (87.69)	
HCV	1 (0.82)	1 (1.30)				
No	17 (13.93)	8 (10.39)		9 (13.85)	8 (12.31)	
Cirrhosis, *n* (%)			0.081			0.861
No	48 (39.34)	40 (51.95)		31 (47.69)	32 (49.23)	
Yes	74 (60.66)	37 (48.05)		34 (52.31)	33 (50.77)	
BCLC stage			0.166			0.979
0–A	87 (71.31)	45 (58.44)		40 (61.54)	41 (63.08)	
B	11 (9.02)	9 (11.69)		8 (12.31)	8 (12.31)	
C	24 (19.67)	23 (29.87)		17 (26.15)	16 (24.62)	
Types of hepatectomy, *n* (%)			0.360			0.860
Anatomical	60 (49.18)	43 (55.84)		34 (52.31)	35 (53.85)	
Non-anatomical	62 (50.82)	34 (44.16)		31 (47.69)	30 (46.15)	
Tumor size, *n* (%)			**0.022**			0.714
≤ 5 cm	58 (47.54)	24 (31.17)		22 (33.85)	24 (36.92)	
> 5 cm	64 (52.46)	53 (68.83)		43 (66.15)	41 (63.08)	
Tumor number, *n* (%)			0.993			0.517
Single	95 (77.87)	60 (77.92)		53 (81.54)	50 (76.92)	
Multiple	27 (22.13)	17 (22.08)		12 (18.46)	15 (23.08)	
Edmondson–Steiner grade, *n* (%)			0.370			0.860
III/IV	65 (53.28)	36 (46.75)		30 (46.15)	31 (47.69)	
I/II	57 (46.72)	41 (53.25)		35 (53.85)	34 (52.31)	
MVI, *n* (%)			0.055			1.000
No	58 (47.54)	26 (33.77)		25 (38.46)	25 (38.46)	
Yes	64 (52.46)	51 (66.23)		40 (61.54)	40 (61.54)	
Macrovascular invasion, *n* (%)			0.123			0.833
No	100 (81.97)	56 (72.73)		51 (78.46)	50 (76.92)	
Yes	22 (18.03)	21 (27.27)		14 (21.54)	15 (23.08)	

Table 1 (continued)

Variable	Before PSM			After PSM		
	No-PD-1 ($n=122$)	PD-1 ($n=77$)	p	Non-PD-1 ($n=65$)	PD-1 ($n=65$)	p
Capsular invasion, *n* (%)			0.815			0.545
No	89 (72.95)	55 (71.43)		50 (76.92)	47 (72.31)	
Yes	33 (27.05)	22 (28.57)		15 (23.08)	18 (27.69)	
Satellite nodules, *n* (%)			0.457			0.708
No	81 (66.39)	55 (71.43)		43 (66.15)	45 (69.23)	
Yes	41 (33.61)	22 (28.57)		22 (33.85)	20 (30.77)	
TACE, *n* (%)			0.169			0.856
No	83 (68.03)	45 (58.44)		41 (63.08)	40 (61.54)	
Yes	39 (31.97)	32 (41.56)		24 (36.92)	25 (38.46)	

PSM propensity score matching, *PD-1* programmed cell death protein-1, *SD* standard deviation, *WBC* white blood cell, *PLT* platelet, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALBI* albumin–bilirubin, *AFP* alpha-fetoprotein, *DCP* des-γ-carboxy prothrombin, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *BCLC* Barcelona Clinic Liver Cancer, *MVI* microvascular invasion, *TACE* transarterial chemoembolization

the PD-1 inhibitors group and 42.0 months (IQR: 39.6–44.4) for the non-PD-1 inhibitors group. Before PSM, the median RFS in PD-1 inhibitors group did not reach, while it was 12.0 (6.7–17.3) months in non-PD-1 inhibitors group. The corresponding 1-year and 2-year RFS were 86.9% and 73.1% in the PD-1 inhibitors group compared with 49.2% and 36.8% in non-PD-1 inhibitors group, respectively ($p<0.001$, Fig. 2A). The median OS in two groups both did not reach. The corresponding 1-year and 2-year OS were 98.7% and 96.6% in the PD-1 inhibitors group compared with 92.6% and 80.8% in non-PD-1 inhibitors group, respectively ($p=0.02$, Fig. 2B).

After PSM, the median RFS in PD-1 inhibitors group did not reach, while it was 11.0 (8.0–14.0) months in non-PD-1 inhibitors group. The corresponding 1-year and 2-year RFS were 87.1% and 74.2% in the PD-1 inhibitors group compared with 44.6% and 37.8% in non-PD-1 inhibitors group, respectively ($p<0.001$, Fig. 2C). The median OS in two groups both did not reach. The corresponding 1-year and 2-year OS were 98.5% and 95.7% in the PD-1 inhibitors group compared with 90.7% and 77.0% in non-PD-1 inhibitors group, respectively ($p=0.004$, Fig. 2D).

Prognostic factors of RFS and OS

The multivariable analysis conducted before PSM identified macrovascular invasion (HR = 2.92; 95% CI 1.76–4.87; $p<0.001$), satellite nodules (HR = 1.73; 95% CI 1.11–2.69; $p=0.016$), the use of adjuvant PD-1 inhibitors (HR = 0.18; 95% CI 0.10–0.30; $p<0.001$) and TACE (HR = 0.22; 95% CI 0.13–0.37; $p<0.001$) as independent prognostic factors for RFS (Table S1). In terms of OS, multivariable analysis revealed that macrovascular invasion (HR = 8.50; 95% CI 4.19–17.23; $p<0.001$), satellite nodules (HR = 2.21; 95% CI 1.13–4.33; $p=0.002$), adjuvant PD-1 inhibitors (HR = 0.18; 95% CI 0.07–0.45; $p<0.001$) and TACE (HR = 0.22; 95% CI 0.09–0.53; $p<0.001$) were independent factors of OS (Table S2).

After PSM, multivariable analysis revealed macrovascular invasion (HR = 3.17; 95% CI 1.73–5.48; $p<0.001$), adjuvant PD-1 inhibitors (HR = 0.15; 95% CI 0.08–0.29; $p<0.001$) and TACE (HR = 0.23; 95% CI 0.12–0.46; $p<0.001$) were independent factors of RFS (Table 2). In terms of OS, multivariable analysis revealed that macrovascular invasion (HR = 6.21; 95% CI 2.55–15.12; $p<0.001$), adjuvant PD-1 inhibitors (HR = 0.14; 95% CI 0.04–0.49; $p=0.002$) were independent factors of OS (Table 3).

Subgroup analysis

The subgroup analysis of RFS and OS is shown in Fig. 3. The results indicated that adjuvant PD-1 inhibitors group consistently achieved longer RFS than the non-PD-1 inhibitors group in patients without adjuvant TACE (HR = 0.14; 95% CI 0.07–0.28; $p=0.004$). No significant differences were observed in the OS subgroup analysis.

Safety

A summary of adverse events in the 77 patients who received adjuvant PD-1 inhibitors is presented in Table 4. Adverse events were reported in 32 patients (41.6%), with the majority being grades 1/2 (28.6%) and a minority being grades 3/4 (13.0%). The most common adverse events included pruritus (13.0%), rash (7.8%), diarrhea (7.8%), and elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) (3.9%). There were no treatment-related fatalities within the PD-1 inhibitors group.

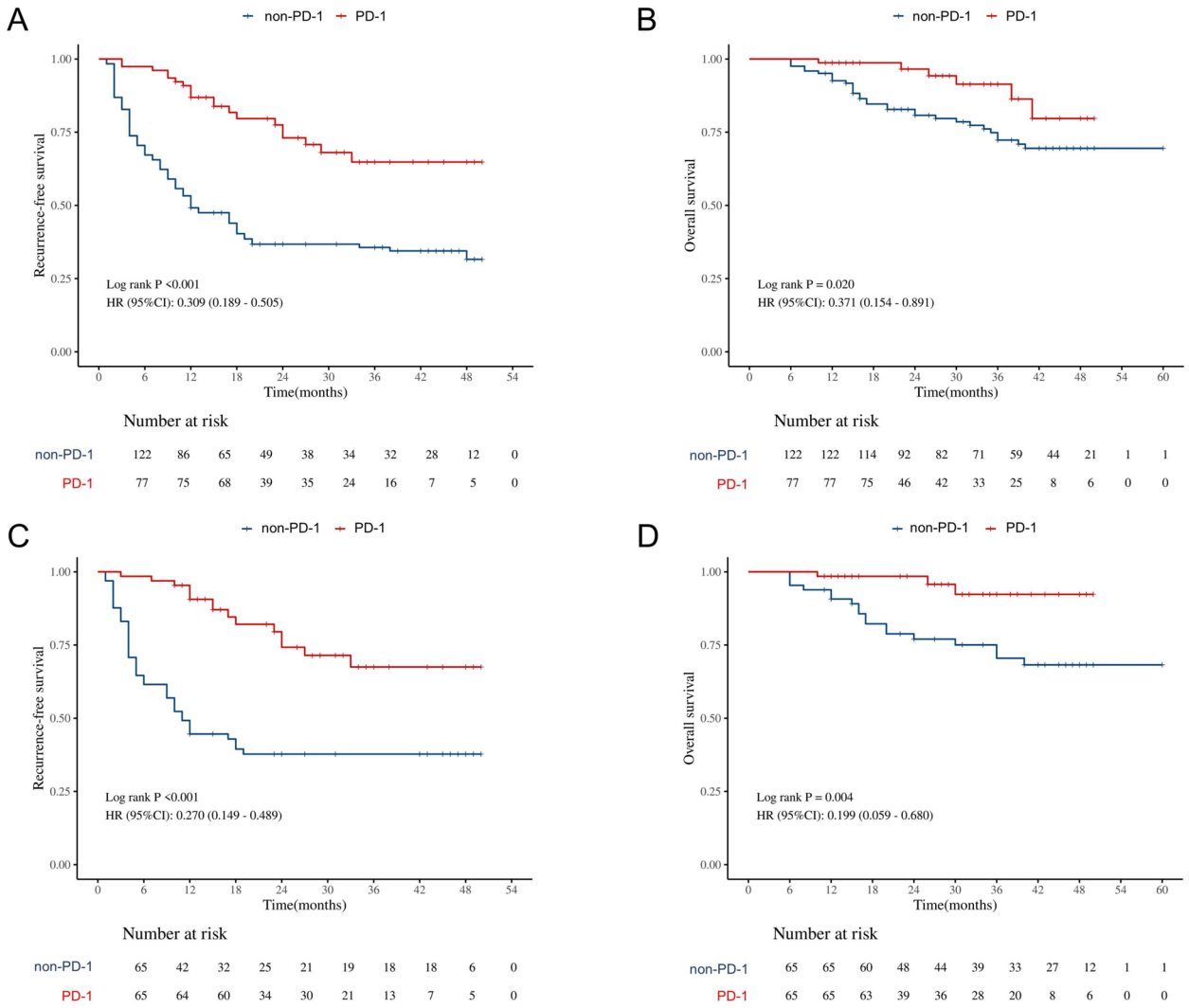

Fig. 2 Survival analysis of RFS and OS in two groups before PSM (**A**, **B**) and after PSM (**C**, **D**). *RFS* recurrence-free survival, *OS* overall survival, *PSM* propensity score matching; *HR* hazard ratio

Discussion

HCC management primarily relies on surgical resection, yet the high recurrence rate post-hepatectomy leads to suboptimal survival outcomes [25]. Patients undergoing hepatectomy for HCC anticipate reduced recurrence and extended survival, prompting investigations into postoperative adjuvant therapies. ICIs, particularly PD-1 inhibitors, have shown promise in advanced HCC and are being explored for their potential in adjuvant settings. Mechanistically, PD-1 inhibitors can restore antitumor immunity by preventing T cell inactivation [26]. A multicenter, open-label, randomized, controlled phase II trial demonstrated the efficacy of sintilimab in postoperative adjuvant treatment for HCC patients with MVI [15]. However, the updated analysis of IMbrave050 (after a median follow-up of 35.1 months) reported that the initial RFS benefit with atezolizumab + bevacizumab vs active surveillance was not sustained [27]. Therefore, the current adjuvant PD-1 inhibitor for HCC remains challenging, it is imperative to investigate effective strategies for adjuvant immunotherapy and identify the appropriate patients in the next five years. Several other clinical trials of adjuvant PD-1 inhibitor treatment for HCC are ongoing, such as pembrolizumab (NCT03867084) and nivolumab (NCT03383458), we eagerly anticipate the results of these trials.

In our study, survival analysis demonstrated patients in PD-1 inhibitors group had better RFS and OS than those in non-PD-1 inhibitors group after PSM. Compared to non-PD-1 inhibitors group, adjuvant PD-1 inhibitors

Table 2 Univariate and multivariate analysis of RFS after PSM

Variable	Univariate			Multivariate		
	HR	95%CI	*p*	HR	95%CI	*p*
Sex (female vs male)	1.08	0.49–2.40	0.843			
Age (years, ≥ 60 vs < 60)	0.59	0.32–1.09	0.091			
ALT (U/L, ≥ 40 vs < 40)	1.22	0.64–2.32	0.543			
AST (U/L, ≥ 40 vs < 40)	1.53	0.86–2.75	0.149			
ALBI grade (2/3 vs 1)	0.91	0.45–1.86	0.800			
AFP (ng/mL, ≥ 400 vs < 400)	1.69	0.98–2.92	0.058			
DCP (mAU/mL, ≥ 40 vs < 40)	1.35	0.73–2.52	0.341			
Viral infection (yes vs no)	1.59	0.63–3.99	0.322			
Cirrhosis (yes vs no)	1.36	0.80–2.33	0.260			
Tumor size (cm, > 5 vs ≤ 5)	1.33	0.74–2.38	0.341			
Tumor number (multiple vs single)	1.09	0.57–2.06	0.799			
Edmondson–Steiner grade (I/II vs III/IV)	0.98	0.58–1.66	0.936			
MVI (yes vs no)	1.42	0.81–2.50	0.218			
Macrovascular invasion (yes vs no)	2.13	1.21–3.75	0.009	3.17	1.73–5.84	< 0.001
Capsular invasion (yes vs no)	0.9	0.49–1.65	0.072			
Satellite nodules (yes vs no)	1.32	0.76–2.27	0.324			
PD-1 inhibitors (yes vs no)	0.27	0.15–0.49	< 0.001	0.15	0.08–0.29	< 0.001
TACE (yes vs no)	0.34	0.18–0.66	0.002	0.23	0.12–0.46	< 0.001

RFS recurrence-free survival, *PSM* propensity score matching, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALBI* albumin–bilirubin, *AFP* alpha-fetoprotein, *DCP* des-γ-carboxy prothrombin, *MVI* microvascular invasion, *PD-1* programmed cell death protein-1, *TACE* transarterial chemoembolization

Table 3 Univariate and multivariate analysis of OS after PSM

Variable	Univariate			Multivariate		
	HR	95%CI	*p*	HR	95%CI	*p*
Sex (female vs male)	1.32	0.39–4.48	0.657			
Age (years, ≥ 60 vs < 60)	1.53	0.64–3.64	0.334			
ALT (U/L, ≥ 40 vs < 40)	0.70	0.21–2.39	0.575			
AST (U/L, ≥ 40 vs < 40)	1.62	0.65–4.03	0.297			
ALBI grade (2/3 vs 1)	0.78	0.26–2.32	0.655			
AFP (ng/mL, ≥ 400 vs < 400)	0.98	0.38–2.54	0.972			
DCP (mAU/mL, ≥ 40 vs < 40)	1.02	0.40–2.64	0.962			
Viral infection (yes vs no)	0.79	0.23–2.69	0.708			
Cirrhosis (yes vs no)	0.83	0.35–1.95	0.662			
Tumor size (cm, > 5 vs ≤ 5)	0.80	0.33–1.94	0.629			
Tumor number (multiple vs single)	0.87	0.29–2.60	0.807			
Edmondson–Steiner grade (I/II vs III/IV)	1.26	0.53–2.98	0.605			
MVI (yes vs no)	2.07	0.76–5.65	0.155			
Macrovascular invasion (yes vs no)	5.36	2.25–12.73	< 0.001	6.21	2.55–15.12	< 0.001
Capsular invasion (yes vs no)	0.73	0.27–1.99	0.536			
Satellite nodules (yes vs no)	2.37	1.01–5.57	0.049	1.88	0.78–4.50	0.157
PD-1 inhibitors (yes vs no)	0.20	0.06–0.68	0.010	0.14	0.04–0.49	0.002
TACE (yes vs no)	0.53	0.19–1.45	0.215			

OS overall survival, *PSM* propensity score matching, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ALBI* albumin–bilirubin, *AFP* alpha-fetoprotein, *DCP* des-γ-carboxy prothrombin, *MVI* microvascular invasion, *PD-1* programmed cell death protein-1, *TACE* transarterial chemoembolization

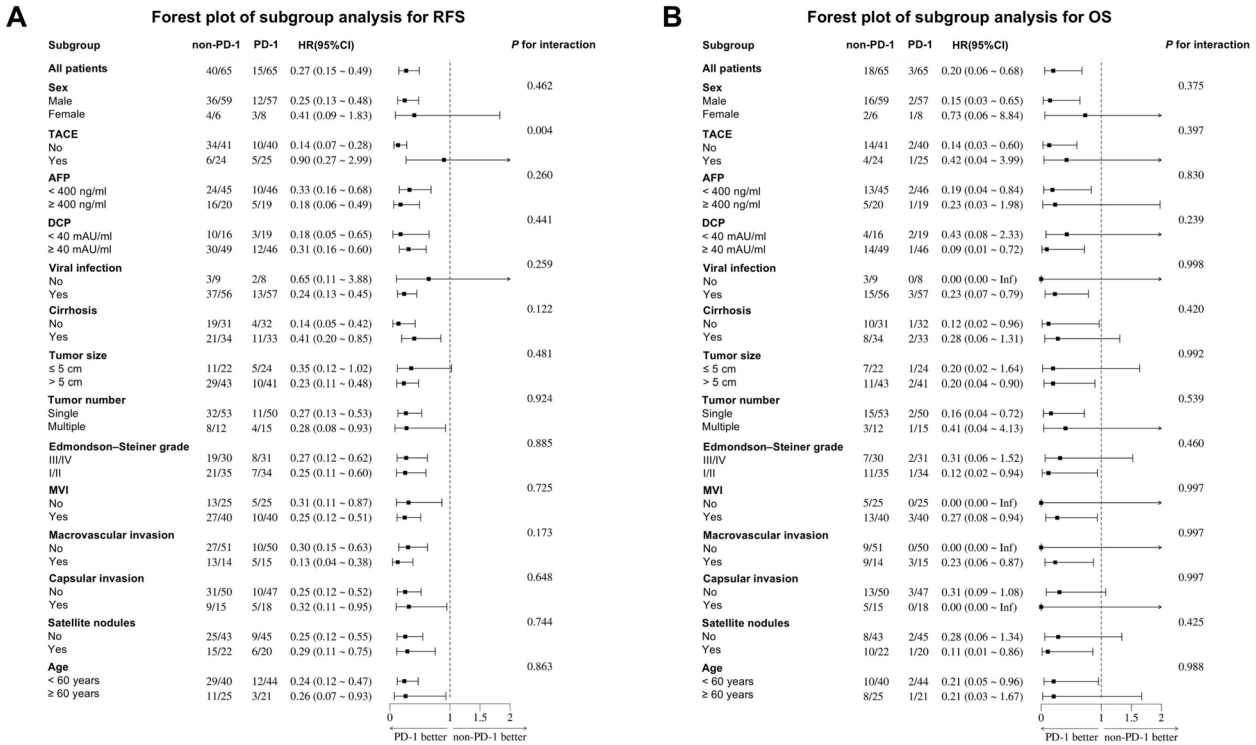

Fig. 3 Subgroup analysis of RFS (**A**) and OS (**B**) after PSM. RFS, recurrence-free survival; OS, overall survival; PSM, propensity score matching; HR, hazard ratio

Table 4 Summary of patient safety in the PD-1 inhibitors group before PSM

Adverse events	All grades, *n* (%)	Grade 1–2, *n* (%)	Grade 3–4, *n* (%)
All patients	32 (41.6)	22 (28.6)	10 (13.0)
Rash	6 (7.8)	4 (5.2)	2 (2.6)
Pruritus	10 (13.0)	7 (9.1)	3 (3.9)
Hypertension	2 (2.6)	1 (1.3)	1(1.3)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	6 (7.8)	5 (6.5)	1(1.3)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)
Proteinuria	1 (1.3)	1 (1.3)	0 (0.0)
Elevated ALT/AST	3 (3.9)	2 (2.6)	1 (1.3)
Elevated bilirubin	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	3 (3.9)	1 (1.3)	2 (2.6)
Anemia	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)
Decreased neutrophils	1 (1.3)	1 (1.3)	0 (0.0)

PD-1 programmed cell death protein-1, *PSM* propensity score matching, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase

could effectively improve the 1-year and 2-year RFS of HCC patients with high-risk recurrence factors. In addition, univariable and multivariable analysis revealed that PD-1 inhibitors treatment was an independent factor for RFS and OS, this finding aligns with the findings of Li who demonstrated that ICIs could improve survival prognosis of patients with high risk of recurrence after curative resection [28]. The finding of the present study suggests that adjuvant treatment of PD-1 inhibitors has great potential in reducing recurrence of HCC patients with high-risk recurrence factors. However, the median RFS and OS for the PD-1 inhibitors group were not

reached within the study period, indicating the need for extended follow-up to ascertain the long-term efficacy of adjuvant PD-1 inhibitors fully. In addition, outcomes observed in the non-PD-1 inhibitors group in our study were worse compared with those from the IMbrave050 trial, which might be due to differences in selection criteria and clinical background. The IMbrave050 trial enrolled patients who underwent either hepatectomy or ablation, whereas our study did not enroll patients who underwent ablation. Moreover, 24.62% (16/65) of patients in the non-PD-1 inhibitors group were at C stage of BCLC after PSM in our study, compared to 7% (22/334) in the IMbrave050 trial [29].

Macrovascular invasion emerged as a significant prognostic factor for both RFS and OS in our analysis, highlighting its detrimental impact on HCC patient outcomes. This finding aligns with global observations, emphasizing the need for tailored treatment strategies for patients presenting with this feature [30]. In contrast to the guidelines followed in Western countries [31], our study included patients with macrovascular invasion who underwent resection because a considerable number of HCC patients were diagnosed advanced stage in China and liver resection combined with thrombectomy remains a common treatment in selected patients with macrovascular invasion. According to the clinical guidelines from China and other research from Asian centers, patients with macrovascular invasion could still achieve favorable outcomes [32, 33]. However, the potential influence of variations in guidelines across Western and Asian nations on the generalizability of the findings should be noted.

Since adjuvant TACE has been incorporated in liver cancer diagnosis and treatment guidelines of China, patients who received one cycle of TACE following resection were not excluded in this study [23]. Our multivariable analysis revealed that TACE was an independent factor for RFS of HCC patients with high-risk factors both before and after PSM. Notably, Subgroup analysis also demonstrated that adjuvant PD-1 inhibitors group achieved longer RFS than the non-PD-1 inhibitors group in patients who had high-risk factors but not received adjuvant TACE. These findings demonstrated patients with high risk of recurrence could benefit from postoperative adjuvant TACE. However, whether PD-1 inhibitors combined with TACE is more effective remains unclear. Li et al. [34] demonstrated that there was no significant difference in TACE alone group and TACE combined with A + T group in reducing the early recurrence of HCC ($p = 0.910$). Huang et al. [35] found the median RFS of TACE + PD-1 inhibitors group was longer than TACE alone in patients with huge HCC ($p = 0.035$). Future randomized controlled trials are needed to explore the efficacy of combinational adjuvant treatment.

This study indicates that adjuvant PD-1 inhibitor following hepatectomy may potentially reduce recurrence of HCC; however, there are several limitations. First, it is a retrospective, single-center study. Second, the relatively short follow-up period also limits the conclusions that can be drawn regarding long-term survival. Third, to date, there is no standardized stratification of recurrence risk factors, potentially leading to differences in effectiveness between this study and other adjuvant PD-1 inhibitor treatments. Fourth, the use of different PD-1 inhibitors in the study may have impacted the consistency of treatment. Therefore, future multicenter, randomized controlled trials with larger cohorts and extended follow-up are necessary to validate these findings and to establish standardized treatment protocols.

Conclusion

In conclusion, our study suggests that adjuvant PD-1 inhibitors could be a valuable addition to the treatment armamentarium for HCC patients at high risk of recurrence post-hepatectomy. Further research is crucial to refine the use of these agents in clinical practice.

Supplementary Information

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Supplementary Material 1.

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Not applicable.

Author contributions
ZYZ and HHD designed the present study. XHS wrote the manuscript. WY, ELZ, ZWZ and ZYZ carried out data and writing analysis segment. ZYZ and HHD revised the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
This retrospective study was conducted in accordance with the Declaration of Helsinki. The study was approved by Ethics Committee of Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology. Written informed consent for participation was not required from the participants because this is a retrospective study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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