Original Article

Adjuvant camrelizumab plus apatinib in resected hepatocellular carcinoma with microvascular invasion: a multi-center real world study

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Background: Hepatocellular carcinoma (HCC) treatment currently lacks adjuvant therapy with a high level of supporting evidence to reduce recurrence after hepatectomy. This study aimed to assess the safety and efficacy of camrelizumab plus apatinib in the adjuvant therapy of patients with HCC with microvascular invasion (MVI).

Methods: Data were retrospectively collected on consecutive patients with HCC who underwent radical resection and were diagnosed with MVI-positive tumors between October 2019 and June 2022 at four centers. The association between adjuvant therapy and prognosis [recurrence-free survival (RFS), overall survival (OS)] was evaluated by propensity score matching (PSM), the log-rank test, Cox regression analysis, and subgroup analysis. Furthermore, grade 3 or 4 treatment-related adverse events (TRAEs) of adjuvant therapy were reported.

Results: Among the 111 patients in the adjuvant therapy group and 276 patients in the observation group

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at enrolment, there were 99 and 172 in the adjuvant therapy and observation groups after PSM, respectively. RFS was better in the adjuvant therapy group [hazard ratio (HR) 0.52; 95% confidence interval (CI): 0.39 to 0.69; P<0.001], whereas OS was not (HR 0.62; 95% CI: 0.39 to 0.99; P=0.079). These results were confirmed after PSM. Subgroup analyses were generally consistent in favour of adjuvant camrelizumab plus apatinib with better RFS. Grade 3 or 4 TRAEs accounted for 20.7% during adjuvant therapy; the most common TRAEs included hypertension and proteinuria.

Conclusions: Postoperative adjuvant camrelizumab plus apatinib significantly improved the RFS benefits with acceptable toxicities in patients with HCC with MVI.

Keywords: Hepatocellular carcinoma (HCC); adjuvant therapy; targeted therapy; immunotherapy

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide, with a relative 5-year survival rate of only 18% (1). Hepatectomy is the main curative therapy for patients with HCC (1). However, over 60% of patients with HCC receiving hepatectomy experience recurrence within five years, limiting the long-term survival of patients with HCC (2,3).

Currently, no recognized adjuvant therapy has been recommended for resected HCC (1,4,5). Optimizing HCC radical therapy using adjuvant therapy, especially in patients with risk factors for recurrence, is particularly significant. Microvascular invasion (MVI) is an acknowledged prognostic factor of HCC, associated with early recurrence and worse outcomes after hepatectomy (6,7). For HCC with MVI, local therapy, including transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC), have been explored as adjuvant therapy and have shown reduced recurrence (8-11).

The systematic therapeutic landscape of HCC has transformed into anti-programmed death-1/programmed death ligand 1 (PD-1/PD-L1) antibody-based combination therapy (1,4). In previous clinical trials, the combination of camrelizumab (a high-affinity, humanized, IgG4-κ PD-1 mAb) and apatinib (a selective VEGFR-2 tyrosine kinase inhibitor) showed promising efficacy and manageable safety in both first-line/second-line setting for unresected HCC and perioperative setting for resected HCC (12-14). Based on these positive outcomes, there is increasing interest in combination therapy for resected HCC. Theoretically, combined antiangiogenic and anti-PD-1/PD-L1 therapy could induce vascular normalization and reprogram the immune microenvironment, improving anti-tumor immunity (15,16). The synergistic effect between antiangiogenic agents and anti-PD-1/PD-L1 antibodies may present a potential postoperative adjuvant strategy for HCC.

However, adjuvant antiangiogenic therapy plus immunotherapy for HCC has not yet been reported. This multicenter real-world study aimed to investigate if camrelizumab plus apatinib as adjuvant therapy could effectively reduce the recurrence of resected HCC with MVI and evaluate the tolerability of the combination. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-363/rc).

Highlight box

Key findings

- Postoperative adjuvant camrelizumab plus apatinib significantly improved the recurrence-free survival benefits with acceptable toxicities in resected hepatocellular carcinoma (HCC) with microvascular invasion (MVI).

What is known and what is new?

- Currently, no recognized adjuvant therapy has been recommended for resected HCC, especially for HCC with MVI.
- This is the first multi-center study to evaluate the efficacy and safety of camrelizumab plus apatinib as adjuvant therapy in resected HCC with MVI.

What is the implication, and what should change now?

- The HCC with MVI can safely receive postoperative adjuvant camrelizumab plus apatinib.

Methods

This study was registered in the Research Registry (Research Registry UIN: researchregistry9117). Research procedures were conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 19-010). All participating institutions were informed and agreed with the study. Informed consents for the treatment and the use of data for research purposes were obtained from all screened patients.

Patients

This multicenter real-world study was conducted at three public tertiary care hospitals in China (Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou; Cancer Hospital, Chinese Academy of Medical Sciences, Beijing; Shandong Cancer Hospital and Institute, Jinan). We collected data from a clinical trial (NCT03839550). We retrospectively collected data on consecutive patients with HCC who underwent radical resection and were diagnosed with MVI-positive tumors by pathology between October 2019 and June 2022. MVI was defined as a microscopic tumor invasion identified in the portal and hepatic veins of the surrounding liver tissue contiguous with the tumor edge and confirmed histologically in the resected specimens.

Inclusion criteria were as follows: HCC with MVI confirmed by postoperative histopathology; preoperative treatment-naïve; no macrovascular invasion and extrahepatic metastasis; hepatectomy and adjuvant therapy undergone at the authors' centers; no evidence of residual or recurrent tumor by postoperative radiological follow-up (4–6 weeks after hepatic resection). Exclusion criteria were as follows: positive resection margin (R1 resection) proved by the postoperative histopathology; severe postoperative complications; loss of follow-up within 6 months. This work has been reported in line with the STROBE criteria (17).

Interventions, follow-up, and outcomes

Surgical oncologists, with at least 10 years of experience in hepatobiliary surgery, executed all surgical procedures. All patients were re-examined in each hospital 4–6 weeks after hepatectomy. If no recurrence was found, adjuvant therapy was recommended due to the pathologic MVI. The adjuvant regimen involved intravenous administration of camrelizumab (Hengrui Pharmaceuticals Co., Ltd.; Lianyungang, China) 200 mg every 3 weeks plus oral administration of apatinib (Hengrui Pharmaceuticals Co.) 200 mg/day. Therapeutic decisions were made via discussions with a multidisciplinary team (MDT), including surgical oncologists, medical oncologists, pathologists, and radiologists. The acceptance of therapeutic recommendations depended on the socioeconomic status of the patients or compliance with the doctors of MDT. For patients who followed the therapeutic recommendations, adjuvant therapy started at 6–8 weeks post hepatectomy and continued until tumor recurrence or metastasis was observed, intolerable toxicity occurred, or camrelizumab was intravenously administered 12 times, whichever occurred first.

The first follow-up occurred 4–6 weeks after hepatectomy, then once every 2–3 months for the first two years. Thereafter, follow-up visits were performed every 6 months. Each follow-up visit included laboratory and radiological examinations. For patients with chronic hepatitis B virus (HBV) or chronic hepatitis C virus (HCV) infection or both, appropriate antiviral therapy with nucleotide analogues (NAs) or direct-acting antiviral agents (DAAs) was administered before and after hepatectomy. Appropriate therapeutic regimens were performed based on MDT discussion if tumor recurrence or treatment-related adverse events (TRAEs) occurred. All patients were censored for the final time on 1 October 2022.

The primary outcome was recurrence-free survival (RFS). Secondary outcomes included overall survival (OS) and safety. RFS was defined as the interval from the date of surgery to the date of recurrence or death, whichever occurred earlier, or the last follow-up if recurrence or death did not occur. OS was defined as the interval from the date of surgery to the date of death or last follow-up if death did not occur.

Clinicopathological variables

Clinicopathological variables related to the patient, tumor, and treatment were collected retrospectively from patient records, namely age; sex; etiology of liver disease; presence of cirrhosis; Child-Pugh class; Barcelona Clinic Liver Cancer (BCLC) stage; tumor number; maximum tumor size; Edmondson-Steiner grade; satellite lesions; types of hepatectomy; extent of hepatectomy; preoperative levels of serum α-fetoprotein (AFP), alanine aminotransferase

(ALT), aspartate aminotransferase (AST), and serum albumin (ALB); total bilirubin (TBIL) levels; and history of adjuvant therapy. Cirrhosis was confirmed by histopathological examination of the noncancerous part of the resected specimens. Major hepatectomy was defined as the resection of three or more Couinaud segments, whereas minor hepatectomy was defined as the resection of fewer than three Couinaud segments. Anatomical resections were defined by the Brisbane 2000 nomenclature of liver anatomy, whereas non-anatomical resections included wedge resection or limited resection (18).

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. was used to evaluate the safety of adjuvant therapy. The severity of TRAEs was divided into five grades. The detailed criteria for these TRAEs were the following: Grade I Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade II Moderate: minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Grade III Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Grade IV Life-threatening consequence: urgent intervention indicated. Grade V Death: related to TRAEs.

Statistical analysis

Data on baseline characteristics were presented using descriptive statistics. Categorical variables were expressed as frequency (percentages) and compared using Fisher's exact test or χ^2 test; continuous variables were expressed as median (interquartile range) and compared using the Mann-Whitney test, as appropriate. In order to mitigate the influence of selection bias and possible confounding variables arising from disparate adjuvant therapy and observation groups, researchers employed logistic regression for propensity score matching (PSM) analysis with a calliper size of 0.1, incorporating age, sex, viral hepatitis, cirrhosis, Child-Pugh class, types of hepatectomy, extent of hepatectomy, BCLC stage, tumor number, maximum tumor size, Edmondson-Steiner grade, satellite lesion, levels of AFP, ALT, AST, ALB, and TBIL variables for 1:2 nearest-neighbour matching. The balance in baseline characteristics between the two groups was assessed before and after propensity score weighting and matching using the standardised mean difference (SMD), with values below 0.1 indicating well balance (19). Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using Cox regression models. Variables with a P<0.05 on univariable analysis were selected for multivariable analysis. Data were analysed using R, version 4.2.1 (R Foundation for Statistical Computing; Vienna, Austria). Statistical significance was set at a two-tailed P value <0.05.

Results

Patient characteristics

According to inclusion and exclusion criteria, 387 MVI-positive patients with HCC were included in this study—111 patients receiving postoperative adjuvant therapy and 276 patients under postoperative observation. In the adjuvant therapy group, 73 patients completed the therapeutic programme according to the MDT protocol; 15 patients with III–IV grade TRAEs and 23 patients with tumor recurrence or metastasis during the adjuvant therapy period did not complete the adjuvant therapeutic program. The flow of patient disposition is summarised in *Figure 1*.

After 1:2 PSM analysis, 99 patients were in the adjuvant therapy group and 172 patients were in the observation group. All variates had a SMD <0.1 after PSM and the two groups were well comparable (*Table 1*, Figures S1,S2).

Efficacy analysis

In the whole cohort, median RFS was not reached in the adjuvant therapy group, with 1- and 2-year RFS rates of 64.7% and 54.5%, respectively. The observation group had a median RFS of 11.7 months [95% confidence interval (CI): 8.1–16.5] and 1- and 2-year RFS rates of 49.2% and 36.0%, respectively. For every three patients receiving adjuvant therapy, one recurrence was effectively prevented [number needed to treat (NNT) 2.85; 95% CI: 2.20 to 4.02; P<0.001]. Adjuvant therapy was associated with better RFS than postoperative observation [hazard ratio (HR) 0.52; 95% CI: 0.39 to 0.69; P<0.001; *Figure 2A*]. Median OS was not reached in the adjuvant therapy group, with 1- and 2-year OS rates of 91.9% and 66.0%, respectively. The median OS was not reached in the observation group, with 1- and 2-year OS rates of 81.1% and 69.7%, respectively. For every five patients receiving adjuvant therapy, one death was effectively prevented (NNT 4.62; 95% CI: 3.19 to

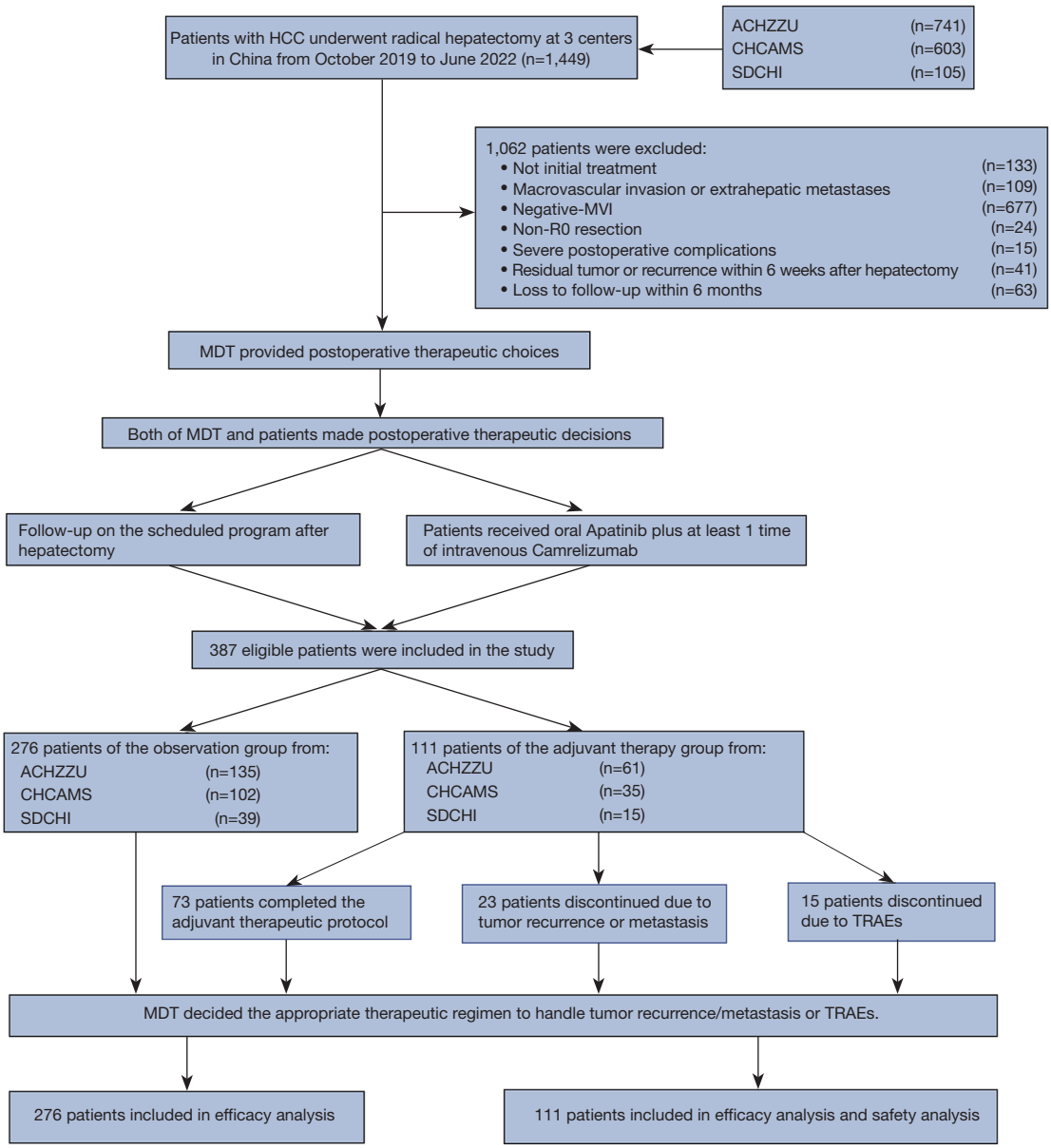

Figure 1 Flow chart of patient selection and therapy. HCC, hepatocellular carcinoma; ACHZZU, Affiliated Cancer Hospital of Zhengzhou University; CHCAMS, Cancer Hospital, Chinese Academy of Medical Sciences; SDCHI, Shandong Cancer Hospital and Institute; MVI, microvascular invasion; R0 resection, no viable or microscopic tumour residue on resection margin; MDT, multidisciplinary team; TRAE, treatment-related adverse event.

8.42; P<0.001). There was no significant difference between the OS of the two groups (HR 0.62; 95% CI: 0.39 to 0.99; P=0.079; *Figure 2B*).

After PSM analysis, the adjuvant therapy group did not reach the median RFS, with a 1- and 2-year RFS rate of 64.1% and 55.1%, respectively. The observation group had a median RFS of 9.3 months (95% CI: 6.5 to 15.1) and 1- and 2-year RFS rates of 46.3% and 33.0%, respectively. For every 3 patients receiving adjuvant therapy, 1 recurrence was effectively prevented (NNT 2.55; 95% CI: 1.98 to 3.59; P<0.001). The adjuvant therapy group showed significantly better RFS than the observation group (HR 0.47; 95% CI: 0.34 to 0.66; P<0.001; *Figure 2C*). Median OS was not reached in the adjuvant therapy group, with 1- and 2-year

Table 1 Baseline characteristics of whole cohort and PSM cohort analyses

Characteristics	Whole cohort			PSM cohort (1:2)		
	Adjuvant therapy group (n=111)	Observation group (n=276)	SMD	Adjuvant therapy group (n=99)	Observation group (n=172)	SMD
Age (years)			0.384			0.093
≤60	83 (74.8)	157 (56.9)		71 (71.7)	116 (67.4)	
>60	28 (25.2)	119 (43.1)		28 (28.3)	56 (32.6)	
Sex			0.100			0.001
Male	95 (85.6)	226 (81.9)		84 (84.8)	146 (84.9)	
Female	16 (14.4)	50 (18.1)		15 (15.2)	26 (15.1)	
Viral hepatitis			0.042			0.027
No	8 (7.2)	17 (6.2)		7 (7.1)	11 (6.4)	
Yes	103 (92.8)	259 (93.8)		92 (92.9)	161 (93.6)	
HBsAg			0.008			0.046
Negative	11 (9.9)	28 (10.1)		9 (9.1)	18 (10.5)	
Positive	100 (90.1)	248 (89.9)		90 (90.9)	154 (89.5)	
Anti-HCV			0.059			0.057
Negative	106 (95.5)	260 (94.2)		95 (96.0)	163 (94.8)	
Positive	5 (4.5)	16 (5.8)		4 (4.0)	9 (5.2)	
Cirrhosis			0.136			0.021
No	65 (58.6)	143 (51.8)		58 (58.6)	99 (57.6)	
Yes	46 (41.4)	133 (48.2)		41 (41.4)	73 (42.4)	
Child-Pugh			0.239			0.048
A	106 (95.5)	274 (99.3)		98 (99.0)	171 (99.4)	
B	5 (4.5)	2 (0.7)		1 (1.0)	1 (0.6)	
Types of hepatectomy			0.071			0.083
Anatomical	67 (60.4)	157 (56.9)		61 (61.6)	99 (57.6)	
Non-anatomical	44 (39.6)	119 (43.1)		38 (38.4)	73 (42.4)	
Extent of hepatectomy			0.056			0.064
Major hepatectomy	42 (37.8)	97 (35.1)		37 (37.4)	59 (34.3)	
Minor hepatectomy	69 (62.2)	179 (64.9)		62 (62.6)	113 (65.7)	
BCLC stage			0.065			0.003
0 + A	94 (84.7)	240 (87.0)		87 (87.9)	151 (87.8)	
B	17 (15.3)	36 (13.0)		12 (12.1)	21 (12.2)	
Number			0.177			0.003
Solitary	86 (77.5)	233 (84.4)		83 (83.8)	144 (83.7)	
Multiple	25 (22.5)	43 (15.6)		16 (16.2)	28 (16.3)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Whole cohort			PSM cohort (1:2)		
	Adjuvant therapy group (n=111)	Observation group (n=276)	SMD	Adjuvant therapy group (n=99)	Observation group (n=172)	SMD
Max size (cm)			0.108			0.044
≤5	42 (37.8)	119 (43.1)		37 (37.4)	68 (39.5)	
>5	69 (62.2)	157 (56.9)		62 (62.6)	104 (60.5)	
Edmonson tumor grade			0.049			0.020
I–II	73 (65.8)	175 (63.4)		66 (66.7)	113 (65.7)	
III–IV	38 (34.2)	101 (36.6)		33 (33.3)	59 (34.3)	
Satellite lesion			0.069			0.068
No	93 (83.8)	238 (86.2)		84 (84.8)	150 (87.2)	
Yes	18 (16.2)	38 (13.8)		15 (15.2)	22 (12.8)	
AFP (ng/mL)			0.049			0.081
≤400	71 (64.0)	170 (61.6)		60 (60.6)	111 (64.5)	
>400	40 (36.0)	106 (38.4)		39 (39.4)	61 (35.5)	
ALT (U/L)	29.0 (23.0–39.4)	26.0 (19.0–45.0)	0.081	29.0 (21.5–40.8)	26.0 (19.0–44.0)	0.031
AST (U/L)	29.0 (24.0–43.0)	33.0 (22.0–49.3)	0.223	29.9 (24.5–42.9)	30.5 (22.0–42.0)	0.009
ALB (g/L)	41.7 (38.7–44.7)	42.7 (39.1–45.7)	0.146	41.7 (38.8–44.7)	42.4 (39.1–45.2)	0.098
TBIL (μmol/L)	13.9 (10.4–18.3)	13.4 (10.3–17.4)	0.115	13.8 (10.2–17.5)	13.3 (9.9–16.8)	0.040

Values are presented as n (%) and median (interquartile range). SMD of less than 0.15 indicates acceptable balance. PSM, propensity score matching; SMD, standardized mean difference; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; AFP, fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin.

OS rates of 90.8% and 64.6%, respectively. The median OS of the observation group was 35.1 months; 95% CI: 34.0 to not estimable), with 1- and 2-year OS rates of 84.6% and 73.0%, respectively. For every six patients receiving adjuvant therapy, 1 death was effectively prevented (NNT 5.11; 95% CI: 3.31 to 11.22; P=0.001). The difference in OS was not significant between the two groups (HR 0.79; 95% CI: 0.46 to 1.36; P=0.409; *Figure 2D*).

In the PSM cohort, 155 patients experienced recurrence, of which 123 (79.4%) were in the observation group and 32 (20.6%) in the adjuvant therapy group. There were 25 (78.1%) cases of intrahepatic recurrence, 3 (9.4%) cases of portal vein tumor thrombosis (PVTT), and 5 (15.6%) cases of extrahepatic metastasis in the adjuvant therapy group; and in the observation group, there were 98 (79.7%) cases of intrahepatic recurrence, 16 (13.0%) cases of PVTT, and 31 (25.2%) cases of extrahepatic metastasis. The patterns of recurrence were similar between the two groups (Table S1).

The subsequent antitumor treatments received by the patients with recurrence in the adjuvant therapy and observation groups were presented in Table S2. These patients were classified according to the time to recurrence of 0–6 months, 7–12 months, 13–18 months, 19–24 months, and >24 months. In the PSM cohort, the proportions of recurrence at 0–6 months, 7–12 months, 13–18 months, and 19–24 months were 51.0%, 26.5%, 10.3%, and 5.2%, respectively. The proportions of recurrence at 0–6 months, 7–12 months, 13–18 months, and 19–24 months, respectively, were 54.5%, 19.5%, 10.6%, and 6.5% in the observation group and 37.5%, 53.1%, 9.4%, and 0.0% in the adjuvant therapy group. The percentages of recurrence by time period were shown in Figure S3.

Univariable and multivariable analysis

Univariate and multivariate analyses of RFS and OS after

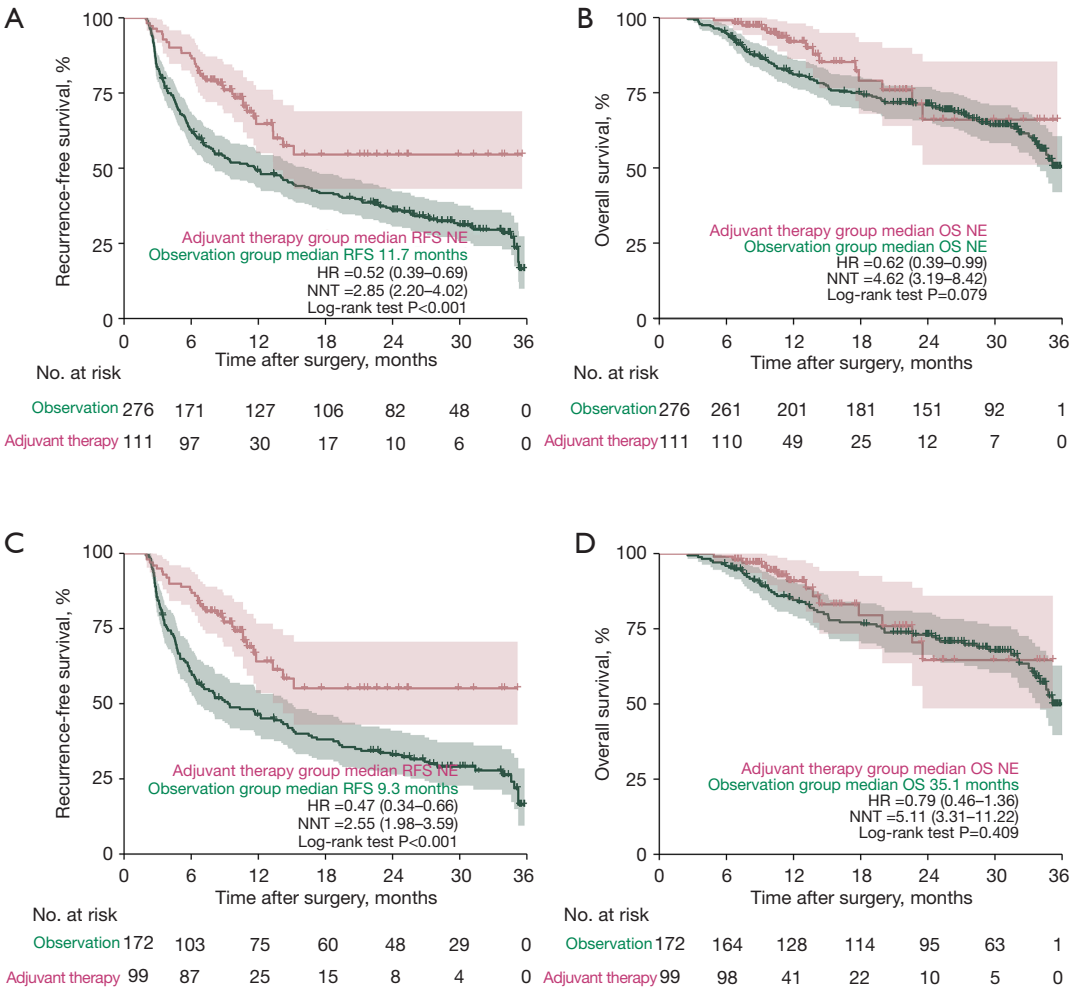

Figure 2 Kaplan-Meier curves of OS and RFS in the whole cohort and the PSM cohort. (A) RFS among patients in the whole cohort. (B) OS among patients in the whole cohort; (C) RFS among patients in the PSM cohort; (D) OS among patients in the PSM cohort. Shaded areas represent 95% confidence intervals. The P value was calculated by using the log-rank test, and HR was calculated by using the Cox proportional hazards regression test. RFS, recurrence-free survival; OS, overall survival; PSM, propensity score matching; NE, not estimable; HR, hazard ratio; NNT, number needed to treat.

PSM analysis are shown in *Table 2*. In univariate analysis, types of hepatectomy, the extent of hepatectomy, BCLC stage, number, max size, Edmondson-Steiner grade, AST level, and postoperative adjuvant therapy were significantly associated with RFS. Multivariate analysis showed that types of hepatectomy (HR 0.48; 95% CI: 0.34 to 0.66; P<0.001), the extent of hepatectomy (HR 1.70; 95% CI: 1.16 to 2.49; P=0.006), BCLC stage (HR 3.50; 95% CI: 1.40 to 8.77; P<0.001), Edmondson-Steiner grade (HR 1.58; 95% CI: 1.14 to 2.21; P=0.007), AST level (HR 1.01; 95% CI: 1.00 to 1.02; P=0.006), and postoperative adjuvant therapy (HR 0.38; 95% CI: 0.25 to 0.56; P<0.001) were independent risk factors for RFS.

Univariate analysis showed that extent of hepatectomy, BCLC stage, number, max size, satellite lesion, and AST level were significantly related to OS. Multivariate analysis showed that extent of hepatectomy (HR 2.13; 95% CI: 1.16 to 3.86; P=0.013) was the only independent risk factor for OS.

Subgroup analysis

Subgroup analysis was performed with stratification of each variable to further explore the impact of adjuvant therapy on postoperative outcomes in MVI-positive patients

Table 2 Univariate and multivariate analysis of RFS and OS for HCC patients with microvascular invasion after PSM

Characteristics	Subgroups	RFS				OS			
		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (years)	≤60	1.02 (0.73–1.43)	0.921			1.30 (0.81–2.09)	0.283		
	>60								
Sex	Male	0.79 (0.52–1.21)	0.276			1.49 (0.74–2.99)	0.267		
	Female								
Viral hepatitis	No	0.66 (0.35–1.22)	0.181			0.59 (0.24–1.37)	0.218		
	Yes								
HBsAg	Negative	0.68 (0.41–1.13)	0.132			0.59 (0.29–1.20)	0.145		
	Positive								
Anti-HCV	Negative	0.79 (0.37–1.68)	0.545			0.77 (0.24–2.44)	0.654		
	Positive								
Cirrhosis	No	0.89 (0.64–1.22)	0.464			0.91 (0.57–1.46)	0.698		
	Yes								
Child-Pugh	A	1.51 (0.21–10.85)	0.680			5.15 (0.71–37.53)	0.106		
	B								
Types of hepatectomy	Anatomical	0.44 (0.32–0.61)	<0.001*	0.48 (0.34–0.66)	<0.001*	0.69 (0.43–1.10)	0.115		
	Non-anatomical								
Extent of hepatectomy	Major hepatectomy	2.13 (1.54–2.93)	<0.001*	1.70 (1.16–2.49)	0.006*	2.71 (1.70–4.32)	<0.001*	2.13 (1.16–3.86)	0.013*
	Minor hepatectomy								
BCLC stage	0 + A	3.37 (2.22–5.11)	<0.001*	3.50 (1.40–8.77)	0.007*	2.34 (1.36–4.04)	0.002*	2.32 (0.49–10.96)	0.289
	B								
Number	Solitary	2.40 (1.64–3.50)	<0.001*	0.97 (0.42–2.24)	0.938	1.83 (1.08–3.10)	0.025*	0.75 (0.17–3.35)	0.706
	Multiple								
Max size (cm)	≤5	1.80 (1.28–2.54)	<0.001*	1.16 (0.75–1.80)	0.498	1.95 (1.15–3.33)	0.014*	1.04 (0.52–2.08)	0.913
	>5								
Edmonson tumor grade	I–II	1.45 (1.05–2.01)	0.023*	1.58 (1.14–2.21)	0.007*	1.43 (0.89–2.30)	0.142		
	III–IV								
Satellite lesion	No	1.48 (0.96–2.28)	0.074			1.88 (1.03–3.44)	0.040*	1.18 (0.62–2.27)	0.611
	Yes								
AFP (ng/mL)	≤400	1.28 (0.92–1.76)	0.141			1.36 (0.85–2.19)	0.197		
	>400								
ALT (U/L)		1.00 (0.99–1.01)	0.613			1.00 (0.99–1.01)	0.275		
AST (U/L)		1.01 (1.00–1.02)	<0.001*	1.01 (1.00–1.02)	0.006*	1.01 (1.00–1.02)	0.014*	1.01 (0.99–1.02)	0.179
ALB (g/L)		0.97 (0.94–1.01)	0.098			0.96 (0.91–1.01)	0.140		
TBIL (μmol/L)		1.02 (0.99–1.05)	0.091			1.04 (0.99–1.07)	0.068		
Adjuvant apatinib plus camrelizumab	No	0.46 (0.31–0.68)	<0.001*	0.38 (0.25–0.56)	<0.001*	0.78 (0.43–1.42)	0.410		
	Yes								

*, P<0.05. Variables with P<0.05 in univariate analysis are entered into multivariate analysis. RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; PSM, propensity score matching; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; AFP, fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin.

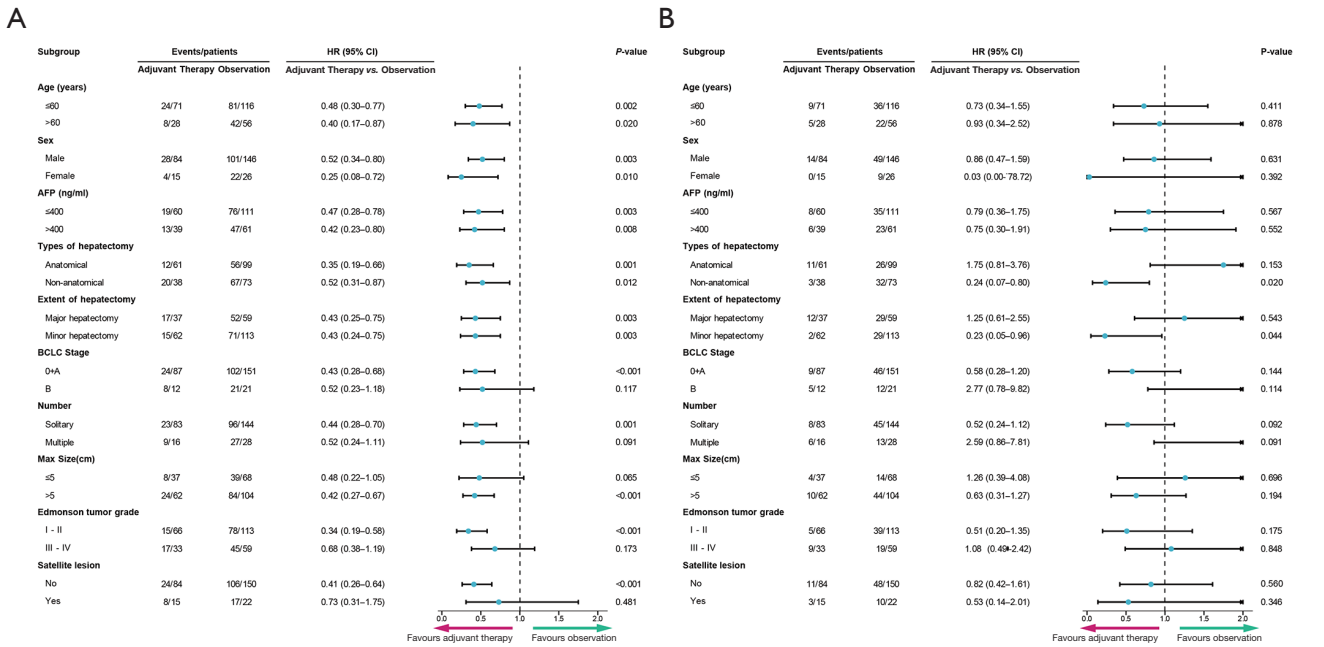

Figure 3 Forest plots by subgroup analysis between the adjuvant therapy and observation groups after PSM. (A) RFS in the PSM cohort. (B) OS in the PSM cohort. PSM, propensity score matching; RFS, recurrence-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; AFP, fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

with HCC. The adjuvant therapy group had similar RFS compared with that of the observation group in subgroups of patients with BCLC B stage, multiple lesions, tumor size ≤5 cm, Edmondson-Steiner grades III–IV, and satellite lesion. The adjuvant therapy group had better RFS than the observation group in subgroups of patients who had BCLC 0 or A stage, single lesion, tumor size >5 cm, Edmondson-Steiner grade I–II, and no satellite lesion and in subgroups of age, sex, AFP level, types of hepatectomy, and extent of hepatectomy (*Figure 3A*). In the subgroup analysis of OS, the adjuvant therapy group only had better OS than the observation group in subgroups of patients who had non-anatomical hepatectomy and minor hepatectomy (*Figure 3B*).

Safety analysis

All 111 patients in the whole cohort were included in the safety analysis, including 23 patients who did not finish the adjuvant therapy programme due to tumor recurrence or metastasis.

In the whole adjuvant therapy group, 90 (81.1%) patients experienced TRAEs, with hypertension (27.9%), proteinuria (23.4%), increased ALT levels (18.0%), increased AST levels (18.0%) being the most common. There were 23 cases (20.7%) of grade 3–4 TRAEs. The most common grade 3 or 4 TRAEs included hypertension (13.5%), proteinuria (11.7%), increased ALT levels (8.1%), increased AST levels (8.1%), and increased TBIL levels (5.4%). Fifteen (13.5%) cases discontinued combination therapy due to TRAEs—7 (6.3%) cases discontinued apatinib, 5 (4.5%) cases discontinued Camrelizumab, and 1 case of immune checkpoint inhibitors (ICIs)-related myocarditis with myositis and 2 cases of ICIs-related pneumonia discontinued both apatinib and Camrelizumab. The remaining patients with all grades of TRAEs had relief after symptomatic treatment. In the adjuvant therapy group, the use of glucocorticoid was counted from the first adjuvant therapy to the last follow-up or death, whichever occurred first. Nine (8.1%) of 111 received systemic glucocorticoid therapy, including 1 case of severe ICIs-related myocarditis with myositis, 2 cases of severe ICIs-related pneumonia, and 6 cases of severe ICIs-related liver injury. No fatal TRAEs occurred (*Table 3*).

Discussion

The combination of anti-angiogenic therapy and

Table 3 Treatment related adverse events in the adjuvant therapy group of the whole cohort

Treatment-related adverse events	Any grade	Grade 1–2	Grade 3	Grade 4
Any treatment-related adverse events	90 (81.1)	67 (60.4)	21 (18.9)	2 (1.8)
Hypertension	31 (27.9)	16 (14.4)	15 (13.5)	0 (0.0)
Proteinuria	26 (23.4)	13 (11.7)	13 (11.7)	0 (0.0)
ALT increased	20 (18.0)	11 (9.9)	9 (8.1)	0 (0.0)
AST increased	20 (18.0)	11 (9.9)	9 (8.1)	0 (0.0)
TBIL increased	14 (12.6)	8 (7.2)	6 (5.4)	0 (0.0)
Thrombocytopenia	11 (9.9)	6 (5.4)	5 (4.5)	0 (0.0)
Rash	9 (8.1)	9 (8.1)	0 (0.0)	0 (0.0)
Hypothyroidism	9 (8.1)	9 (8.1)	0 (0.0)	0 (0.0)
γ-GT increased	9 (8.1)	4 (3.6)	5 (4.5)	0 (0.0)
Neutropenia	8 (7.2)	5 (4.5)	3 (2.7)	0 (0.0)
Leukopenia	5 (4.5)	2 (1.8)	3 (2.7)	0 (0.0)
Hand-foot syndrome	5 (4.5)	5 (4.5)	0 (0.0)	0 (0.0)
Vomiting	5 (4.5)	5 (4.5)	0 (0.0)	0 (0.0)
Fever	5 (4.5)	5 (4.5)	0 (0.0)	0 (0.0)
Diarrhoea	4 (3.6)	4 (3.6)	0 (0.0)	0 (0.0)
Hypoalbuminaemia	4 (3.6)	4 (3.6)	0 (0.0)	0 (0.0)
RCCEP	3 (2.7)	3 (2.7)	0 (0.0)	0 (0.0)
Anaemia	3 (2.7)	3 (2.7)	0 (0.0)	0 (0.0)
Fatigue	3 (2.7)	3 (2.7)	0 (0.0)	0 (0.0)
ALP increased	2 (1.8)	2 (1.8)	0 (0.0)	0 (0.0)
Headache	2 (1.8)	2 (1.8)	0 (0.0)	0 (0.0)
Cough	2 (1.8)	2 (1.8)	0 (0.0)	0 (0.0)
Decreased appetite	2 (1.8)	2 (1.8)	0 (0.0)	0 (0.0)
ICIs-related pneumonia	2 (1.8)	0 (0.0)	1 (0.9)	1 (0.9)
LDH increased	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
Haematuria	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
Arthralgia	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
Myalgia	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
Abdominal pain	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
Hyperglycaemia	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
ICIs-related myocarditis with myositis	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)

Data are presented as n (%). All patients in the adjuvant therapy group of the whole cohort are enrolled in the safety analysis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; γ-GT, γ-glutamyl transferase; RCCEP, reactive cutaneous capillary endothelial proliferation; ALP, alkaline phosphatase; ICI, immune checkpoint inhibitors; LDH, lactate dehydrogenase.

immunotherapy, typified by atezolizumab plus bevacizumab, has been approved as first-line systemic therapy for advanced HCC (4). Camrelizumab plus apatinib has been approved as first-line systemic therapy for unresected HCC by the National Medical Products Administration of China based on the results of SHR-1210-III-310 Trials (NCT03764293) (20). Recently, anti-PD-1/PD-L1 antibody-based systematic therapy has transformed into the perioperative setting, for instance, immunotherapy has been approved as postoperative adjuvant therapy in melanoma, renal cell carcinoma, and non-small cell lung cancer (21-24). However, clinical evidence of postoperative anti-angiogenic therapy plus immunotherapy for resected HCC with MVI is still lacking, although many clinical trials exploring the efficacy of combination therapy are currently ongoing, such as atezolizumab plus bevacizumab (NCT04102098), camrelizumab plus apatinib (NCT04639180), durvalumab alone or combined with bevacizumab (NCT03847428), and tislelizumab alone or combined with sitravatinib (NCT05564338).

As we know, this is the first multicenter real-world study to explore the effect and safety of postoperative adjuvant camrelizumab plus apatinib. After well balance in potential clinical variables affecting tumor recurrence by 1:2 PSM, patients in the adjuvant therapy group had markedly improved RFS but not OS. Furthermore, univariable and multivariable analyses revealed that adjuvant therapy was an independent predictor of RFS rather than OS. RFS benefits cannot translate to OS gains seems to be common in adjuvant therapy after R0 HCC liver resection, such as postoperative adjuvant HAIC with FOLFOX (11). As speculated by Lim *et al.*, longer follow-up or larger sample sizes might show improved OS in patients with HCC (25). A meta-analysis including two randomized controlled trials (RCTs) and nine non-RCTs with 1,290 patients concluded that adjuvant HAIC improves OS in patients with HCC treated with hepatectomy (26). In addition, the survival gains from adjuvant therapy may not be uniform in all patients with HCC after hepatectomy. For patients with HCC and MVI, adjuvant TACE was shown to be significantly associated with improved RFS and OS for those with tumor ≤5 cm, but not for those with tumor >5 cm (27). Therefore, identifying subgroups of benefit is an important way to amplify the value of adjuvant therapy. This is the reason we focused on patients with HCC and MVI. The study demonstrated that for HCC receiving radical resection, patients with late recurrence had better long-term survival than those with early recurrence (28). How RFS benefits from adjuvant therapy translates into OS gains needs to be further proven by long-term results of large sample multicenter prospective clinical trials.

In our study, 1-year OS rates of the adjuvant therapy group and observation group were 90.8% and 84.6% after PSM, respectively. For patients with HCC and MVI, the 10–15% mortality within 1 year after radical resection has been reported in several studies (10,29,30). For patients at high risk of 1-year mortality, postoperative adjuvant therapy may require further discretion. As described by Lim *et al.*, the adjuvant therapy that patients prefer (or even demand) may be a "disease-free" psychological gain that does not result in an actual survival benefit (25). Sheriff *et al.* found that Child-Pugh class B/C, multinodularity, macrovascular invasion, postoperative acute renal failure, and postoperative liver failure were independent risk factors for death within 1 year of HCC receiving hepatectomy (31). The characteristics of these independent risk factors revealed that factors leading to death within 1 year may be broadly classified into two types, recurrence-related factors (multinodularity, macrovascular invasion) and non-recurrence-related factors (Child-Pugh class B/C, renal failure and liver failure). In our study, 7 (7.1%) deaths within 1 year occurred in the adjuvant therapy group and 25 (14.5%) in the observation group. Among these patients, tumor recurrence occurred in 5 (71.4%) in the adjuvant therapy group and 23 (92.0%) in the observation group. Therefore, we considered that adjuvant therapy may have reduced recurrence-related early deaths. As for non-recurrence-related early deaths, prevention and management of serious postoperative complications were critical. For patients at high risk of severe postoperative complications, the combined regimen of non-surgical therapies has been proven to provide a similar prognosis, and to significantly reduce the incidence of major complications, such as liver failure (32). In addition, perioperative steroids administration reduces overall complications and liver failure after hepatectomy (33). However, several studies have shown that patients with tumors receiving immunotherapy who use steroids at baseline or early on have worse prognoses (34,35). Therefore, the combination of perioperative steroids with later ICIs-related adjuvant therapy still needs further exploration.

Through grouping the time to recurrence, we found that the proportions of recurrence decreased with a longer time to recurrence in the whole cohort or the observation group. However, the proportion of patients who recurred at 0–6 months was lower than the proportion of patients who

recurred at 6–12 months in the adjuvant treatment group. We speculate that this was related to the fact that adjuvant therapy reduced the risk of early recurrence. Similar conclusions were confirmed by independent risk factors associated with RFS in patients with HCC with a high risk of recurrence who underwent postoperative adjuvant anti-PD-1 antibody (36). Chen *et al.* considered that independent risk factors associated with RFS in patients with HCC with a high risk of recurrence who were treated with adjuvant anti-PD-1 antibody were consistent with the characteristics of early recurrence (36). Similarly limited by the shorter follow-up in the adjuvant therapy group, the trend for improving early recurrence was not seen in patients with longer recurrence times. Our results demonstrated that adjuvant camrelizumab plus apatinib significantly improved RFS in patients with HCC with MVI.

The immunological context of the tumor microenvironment was expected to have important influences on recurrence risk after hepatectomy. Deficiency of immune effector cells such as $CD3^+$ T, $CD4^+$ T, $CD8^+$ T, Tγδ, and natural killer (NK) cells and accumulation of immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and T regulatory cells (Tregs) were associated with high recurrence rates after hepatectomy (37-42). Reduced infiltration of immune effector cells, accumulation of immunosuppressive cells, and upregulation of immune checkpoints were regulated by VEGF (43-45). Only about 25% of early-stage HCCs showed genetic evidence of immune activation after hepatectomy (46). Combining antiangiogenic and anti-PD-1/PD-L1 therapy was promising to trigger further immune activation to reduce recurrence after hepatectomy. The IMbrave 050 trial (NCT04102098) was a Phase III trial of atezolizumab plus bevacizumab in high-risk HCC after curative resection or ablation (47). This trial was targeted to patients with tumor size >5 cm, tumor number >3, vascular invasion (MVI, Vp1/Vp2 of the portal vein), and poor tumor differentiation (Edmonson tumor grade 3 or 4). Currently, this trial of 668 patients has reported interim analysis results. Similar to our results, atezolizumab plus bevacizumab showed a statistically significant improvement in RFS (HR 0.70; 95% CI: 0.54 to 0.91; P=0.007). Results of subgroup analyses regarding tumor characteristics were generally consistent in favour of adjuvant atezolizumab plus bevacizumab with better RFS, except for BCLC stage B or C, >1 tumor, tumor size ≤5 cm, and Edmonson tumor grade III or IV. These are generally similar to the results of our subgroup analysis. In addition, our subgroup analysis revealed that satellite lesions had no benefit for RFS. This was similar to BCLC stage B or C, >1 tumor, poor tumor differentiation without RFS benefit. However, the specific reasons for these still need to be explored in more detail for different subgroups. The most common grade 3 or 4 adverse events in the adjuvant atezolizumab plus bevacizumab group included hypertension and proteinuria, consistent with our results. The other common, consistent adverse events include thrombocytopenia, increased AST levels, increased ALT levels, and increased TBIL levels (47). Apatinib is a small molecule anti-angiogenesis inhibitor that competitively binds the receptor of intracellular tyrosine adenosine triphosphate and VEGFR-2 to block tumor angiogenesis and promote normalisation of the tumor vessel. A preclinical study has shown that apatinib and camrelizumab cooperate in anti-tumor by blocking the PD-1/PD-L1 and VEGF-VEGFR2 pathways simultaneously. The vascular normalisation effect of apatinib can alleviate the hypoxic state of the tumor microenvironment and restructure the immunosuppressive microenvironment of the tumor, enhancing the anti-tumor immune effect of anti-PD-1/PD-L1 antibodies (48). Chen *et al.* showed that the 1- and 2-year RFS rates in the postoperative adjuvant PD-1 group were 58.40% and 44.13%, respectively, for patients with HCC with a high risk of recurrence (36). Compared to their results, our adjuvant therapy group had better RFS (1- and 2-year RFS rates of 64.1% and 55.1%, respectively). This may be explained by the fact that apatinib and camrelizumab have a stronger anti-tumor effect than that achieved by blocking only the PD-1/PD-L1 pathway by synergistically activating tumor immunity through the simultaneous blockade of the PD-1/PD-L1 and VEGF-VEGFR2 pathways. In addition, our study only emphasised MVI. In contrast, the inclusion criteria of the study by Chen *et al.* included several high risks of recurrence (MVI, portal venous tumor thrombus, hepatic venous tumor thrombus, satellite nodules, tumor nodules >3, AFP >400 ng/mL, maximum tumor size >5 cm). Differences in the baseline of the enrolled patients were also an important factor for the different prognoses. Therefore, the advantages of postoperative adjuvant anti-angiogenic targeted therapy combined with immunotherapy over other postoperative adjuvant options still need further verification in prospective RCTs.

Our study had a few limitations. First, owing to the retrospective nature of our analysis, there were potential biases and confounders. Although we applied PSM to achieve a well-balanced set of clinicopathological

variables (SMD <0.1), some bias was still difficult to avoid completely. Secondly, majority of the patients in our study (92.8%) had viral hepatitis, affecting the universality of our results. Third, the follow-up time of the adjuvant therapy group was significantly insufficient, and the median RFS and OS were not reached. Fourth, some TRAEs, such as hypertension and proteinuria, mainly relied on the patient's subjective descriptions. Patients may have underreported or exaggerated symptoms, and some patients consulted local hospitals for grade 3–4 TRAEs. These factors may have led to bias in the follow-up results of TRAEs.

Conclusions

Postoperative adjuvant camrelizumab plus apatinib significantly improved the RFS benefits with acceptable toxicities in patients with HCC with MVI. Our results need to be further validated by large sample sizes prospective studies to better understand the efficacy and safety of postoperative adjuvant camrelizumab plus apatinib, and the differential effects on early recurrence and late recurrence.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-363/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-363/dss

Peer Review File: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-363/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-363/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was registered in the Research Registry (Research Registry UIN: researchregistry9117). Research procedures were conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Institutional Review Board of Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (No. 19-010). All participating institutions were informed and agreed with the study. Informed consents for the treatment and the use of data for research purposes were obtained from all screened patients.

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