Journal of Clinical and Translational Hepatology **2026** vol. 14(10) | 1003–1014
DOI: 10.14218/JCTH.2026.00283

Original Article

Comparison of Survival Between Patients with Hepatocellular Carcinoma Beyond the "Up-to-7" Criterion Who Received Adjuvant PD-1 Inhibitors or Active Surveillance: A Target Trial Emulation Study

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Received: April 09, 2026 | **Revised:** August 02, 2026 | **Accepted:** August 18, 2026 | **Published online:** September 24, 2026

Abstract

Background and Aims: The IMbrave050 trial suggested that adjuvant immune checkpoint inhibitor therapy may benefit patients with hepatocellular carcinoma exceeding the "up-to-7" criterion. This study aimed to compare survival outcomes and safety between such patients receiving adjuvant programmed cell death protein 1 inhibitors and those undergoing active surveillance after curative resection. ***Methods:*** Data were prospectively collected from patients at 13 medical centers in China between 2019 and 2024. The study was designed according to a target trial emulation framework, and propensity score matching was used to reduce confounding. The primary endpoint was recurrence-free survival; secondary endpoints included overall survival and incidence of treatment-related adverse events. ***Results:*** Median follow-up was 32.7 months (interquartile range, 20.9–47.5). Propensity score matching yielded 200 patients per group. Median recurrence-free survival was longer in the adjuvant group (28.0 months; 95% confidence interval [CI], 21.7–34.3) than in the surveillance group (14.4 months;

Keywords: Adjuvant therapy; Curative resection; Hepatocellular carcinoma; PD-1 inhibitor; "Up-to-7" criterion; Target trial emulation.

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95% CI, 10.7–18.1; hazard ratio, 0.58; 95% CI, 0.45–0.74). Median overall survival was not reached in the adjuvant group and was 45.0 months (95% CI, 37.8–52.1) in the surveillance group (hazard ratio, 0.63; 95% CI, 0.45–0.89). The most frequent grade 3–4 treatment-related adverse events were hand–foot skin reaction (7.2%), elevated alanine aminotransferase (5.8%), and elevated aspartate aminotransferase (5.3%). ***Conclusions:*** Adjuvant programmed cell death protein 1 inhibitors, with or without molecularly targeted agents, were associated with longer recurrence-free survival and acceptable safety in patients with hepatocellular carcinoma exceeding the "up-to-7" criterion.

Citation of this article: Su JY, Liu Z, Yang TX, Guo PP, Luo M, Liu SP, *et al*. Comparison of Survival Between Patients with Hepatocellular Carcinoma Beyond the "up-to-7" Criterion Who Received Adjuvant PD-1 Inhibitors or Active Surveillance: A Target Trial Emulation Study. J Clin Transl Hepatol 2026;14(10):1003–1014. doi: 10.14218/JCTH.2026.00283.

Introduction

Curative hepatectomy is a primary treatment for early-stage hepatocellular carcinoma (HCC) and is also performed in selected patients whose tumors exceed the "up-to-7" criterion, defined as a sum of the number of tumors and maximum tumor diameter (cm) greater than 7.[1] However, more than 70% of patients with HCC who undergo curative resection experience recurrence within 5 years. Patients treated for recurrent disease with repeat resection or ablation may subsequently experience further recurrence.[2] These considerations highlight the need for adjuvant therapies that reduce the risk of postoperative recurrence.[3]

Several adjuvant therapies are used worldwide, but no global consensus exists regarding their efficacy or the patient populations most likely to benefit.[4] A phase II randomized controlled trial suggested that adjuvant anti-programmed cell death protein 1 (PD-1) therapy may reduce recurrence risk,[5] consistent with our prospective cohort studies,[6,7] particularly when treatment was administered for longer than 6 months.[8] In the phase III randomized controlled IMbrave050 trial, adjuvant therapy with a programmed death-ligand 1 (PD-L1) inhibitor plus an angiogenesis inhibitor appeared to reduce recurrence based on interim data,[9] but this effect was not sustained with longer follow-up.[10] Nevertheless, longer-term data suggested a potential survival benefit in patients with HCC exceeding the "up-to-7" criterion.[10] The "up-to-7" criterion integrates tumor size and number to assess postoperative recurrence risk. Patients with greater tumor burden may have a higher likelihood of residual microscopic disease or circulating tumor cells after curative resection, potentially increasing the risk of early recurrence and identifying a population for whom adjuvant immunotherapy warrants further evaluation. Several phase III randomized controlled trials (*e.g.*, CheckMate-9DX and EMERALD-2) are evaluating adjuvant immune checkpoint inhibitor therapy after curative resection, and their results may further clarify its efficacy.

Resolving this controversy is important because uncertainty regarding efficacy may discourage some patients from accepting adjuvant therapy and could limit its appropriate use.[4] Given the cost and logistical challenges of randomized trials, we investigated this question using target trial emulation. In this approach, an observational study is designed to emulate a prespecified randomized trial as closely as possible,[11] and causal-inference methods are applied to estimate treatment effects under the target trial framework.[12,13] We prospectively collected multicenter cohort data from patients whose HCC exceeded the "up-to-7" criterion and who underwent curative resection, and we evaluated whether adjuvant PD-1 inhibitors, with or without molecularly targeted agents, were associated with improved postoperative outcomes.

Methods

Ethical statement

This clinical study was conducted in accordance with the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained from each participant before enrollment, and consent documents were archived. The study protocol received ethical approval from the ethics committees of the 13 participating medical centers in China, with Guangxi Medical University Cancer Hospital in Nanning, China serving as the lead site (LW2021103) and registered at ClinicalTrials.gov (NCT05221398). Preliminary results have been published previously.[6,8]

Study design and patients

Patients were eligible if they underwent hepatectomy at one of 13 participating medical centers in China between January 7, 2019, and December 19, 2024, and met the following criteria: (1) age 18–75 years; (2) HCC exceeding the "up-to-7" criterion based on imaging[1]; (3) R0 resection considered curative as previously defined (Supplementary Table 1)[14]; (4) Eastern Cooperative Oncology Group Performance Status of 0–1 and Child-Pugh score of 5–7 before surgery; and (5) expected survival > 6 months after surgery.

Patients were excluded if, before surgery, they (1) had other malignancies or severe comorbidities affecting vital organs, particularly the brain, heart, or lungs; (2) had received antitumor interventions such as neoadjuvant or conversion therapy; or (3) had macrovascular invasion (Vp3 or Vp4 according to the Liver Cancer Study Group of Japan classification)[15] or extrahepatic metastases. Patients were also excluded if, after surgery, they (4) received adjuvant therapies not involving PD-1 inhibitors, such as tyrosine kinase inhibitor monotherapy, PD-L1 inhibitor therapy, transcatheter arterial chemoembolization, or hepatic arterial infusion chemotherapy; (5) experienced grade 4 or 5 postoperative complications; or (6) developed tumor recurrence within 2 months.

Adjuvant antiviral therapy was not an exclusion criterion.[16]

Hepatectomy

Surgical procedures were performed as previously described.[17]

Adjuvant therapy

Patients decided whether to receive adjuvant therapy after discussion with their family members; attending physicians did not attempt to influence this decision. Adjuvant PD-1 inhibitor therapy was initiated 4–8 weeks after surgery and administered once every 3 weeks for up to 12 months or 18 cycles, unless tumor recurrence or metastasis, intolerable adverse events, protocol deviation, or withdrawal of informed consent occurred. All patients received at least one treatment cycle.

Most patients who received adjuvant PD-1 inhibitors were treated with tislelizumab (BGB-A317; BeOne Medicines, Beijing, China), toripalimab (Shanghai Junshi Biosciences, Shanghai, China), camrelizumab (SHR-1210; Jiangsu HengRui Medicine, Jiangsu, China), sintilimab (IBI308; Innovent Biologics, Suzhou, China), pembrolizumab (Keytruda; Merck, Kenilworth, NJ, USA), or penpulimab (AK105; Akeso,

Zhongshan, China). All inhibitors were administered by intravenous infusion, and dose adjustment was not permitted during treatment. The complete list of PD-1 inhibitors used is provided in Supplementary Tables 2–3.

Tyrosine kinase inhibitors were administered orally, typically beginning concurrently with immunotherapy and continuing once daily. Bevacizumab was given via intravenous infusion according to product labeling. Doses were based on body weight or product labeling. The targeted-drug regimen is presented in Supplementary Table 2. The most frequently used molecularly targeted agents were lenvatinib (Eisai, Woodcliff Lake, NJ, USA), bevacizumab (Genentech, San Francisco, CA, USA), apatinib (Jiangsu HengRui Medicine, Jiangsu, China), donafenib (Suzhou Zejing Biologics, Suzhou, China), and anlotinib (AL3818; Chia Tai Tianqing Pharmaceutical Group, Nanjing, China).

Before treatment, all patients underwent screening that included assessment of general condition, blood tests, and imaging. Because no standard adjuvant treatment protocol was available, regimens were determined by investigators at each center through multidisciplinary assessment of patient characteristics, treatment tolerance, and tumor biology. To improve data consistency, a detailed data-collection manual and centralized quality-control procedures were implemented, and center-specific variation was accounted for in the statistical analysis.

Follow-up and assessment

The first follow-up visit occurred 4–8 weeks after surgery; subsequent visits were scheduled every 3 months for 2 years and every 6 months thereafter. The final follow-up date was June 20, 2025.

Follow-up was primarily conducted on an outpatient basis; patients with complex conditions were admitted when necessary. Each visit included at least a physical examination; hematologic testing, including liver function tests and serum alpha-fetoprotein measurement; assessment of treatment-related adverse events; and liver ultrasonography, contrast-enhanced abdominal computed tomography, or magnetic resonance imaging.

A multidisciplinary team diagnosed HCC recurrence or metastasis based on imaging and/or histopathology; histopathologic confirmation was required in complex cases. Intrahepatic recurrence was assessed and treated according to American Association for the Study of Liver Diseases (AASLD) criteria,[18] whereas extrahepatic metastasis was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[19] HCC recurrence was classified as early (≤ 2 years) or late (> 2 years) according to the interval from curative resection to recurrence.[20] Liver cirrhosis was diagnosed based on postoperative histopathology. Metabolic dysfunction-associated steatotic liver disease (MASLD) was diagnosed from pathology reports and preoperative examinations. Few patients had HCC related to alcohol use or chronic hepatitis C virus infection, whereas most had chronic hepatitis B virus infection. Therefore, HCC etiology-specific subgroup analyses were not performed.

Outcomes

The primary endpoint was recurrence-free survival, defined as the interval from T0 to first recurrence, death from any cause, censoring, or the end of follow-up, whichever occurred first. T0 was defined as the date of treatment initiation (within 4–8 weeks after hepatectomy) after eligibility confirmation for the experimental arm and the date of the first follow-up visit (within 4–8 weeks after hepatectomy) at which curative resection was verified per protocol for the control arm.[14] Under the target-trial-emulation framework, this time-zero definition was implemented to mimic the time-point of randomization in a hypothetical randomized controlled trial. Both arms constrained T0 within the identical 4–8-week window after hepatectomy to align eligibility assessment timing across groups, thereby minimizing immortal-time and selection bias. Secondary endpoints were overall survival, defined as the interval from T0 to death from any cause, censoring, or the end of follow-up, and treatment-related adverse events, which were graded according to the Common Terminology Criteria for Adverse Events, version 5.0.[21]

Emulation of a target trial

We performed and reported the analyses according to the Transparent Reporting of Observational Studies Emulating a Target Trial Statement.[22] The emulation process is detailed in Supplementary Table 4. Appropriate statistical methods were used to compare the treatment strategies of interest. An alternative time point (Td), corresponding to the date of surgery for eligible patients, was also documented for recalculation of recurrence-free and overall survival.

Statistical analysis

Data were analyzed using SPSS 22.0 (IBM, Chicago, IL, USA), GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA), and R 4.4.1 (R Project, Vienna, Austria). Statistical significance was defined as $P < 0.05$, and all tests were two-sided.

Continuous data were assessed for normality using the Shapiro–Wilk test. Normally distributed data were reported as the mean ± standard deviation, and between-group differences were assessed using Student's *t* test when Levene's test indicated equal variances and Welch's *t* test otherwise. Skewed continuous data were reported as the median (interquartile range [IQR]) and were compared using the Mann–Whitney *U* test. Categorical data were reported as frequency (n) and proportion (%) and were compared using Pearson's chi-square test or Fisher's exact test.

All clinical variables were prospectively collected across participating centers using standardized electronic case report forms; the proportion of missing values was <1% for each covariate included in the propensity score matching model. Multiple imputation by chained equations (MICE) was used to impute sparse missing covariate values before propensity score estimation (10 imputed datasets with five iterations per chain). The imputation model included all baseline prognostic predictors, treatment allocation, and survival endpoints. For survival analyses, patients lost to follow-up were treated as censored observations. By contrast, patients without complete recurrence or overall survival outcome data (*i.e.*, no follow-up time recorded) were excluded from the final analytic cohort because complete outcome ascertainment was required for the planned analyses.

The minimum sample size was estimated as 186 patients per group using PASS 15 software (NCSS, Kaysville, UT, USA) (Supplementary Table 4). Primary and secondary outcomes were compared between patients receiving adjuvant PD-1 inhibitors and those undergoing active surveillance in the entire cohort and in 1:1 propensity score-matched subgroups. Potential confounders were identified from the literature and high-quality evidence and selected using a directed acyclic graph (DAG) (Supplementary Fig. 1). The selected variables were entered into a multivariable logistic regression model with treatment as the dependent variable and the following covariates: sex, age, Child-Pugh class, hepatitis B surface antigen (HBsAg) status, alpha-fetoprotein, Eastern Cooperative Oncology Group Performance Status, liver cirrhosis, MASLD,

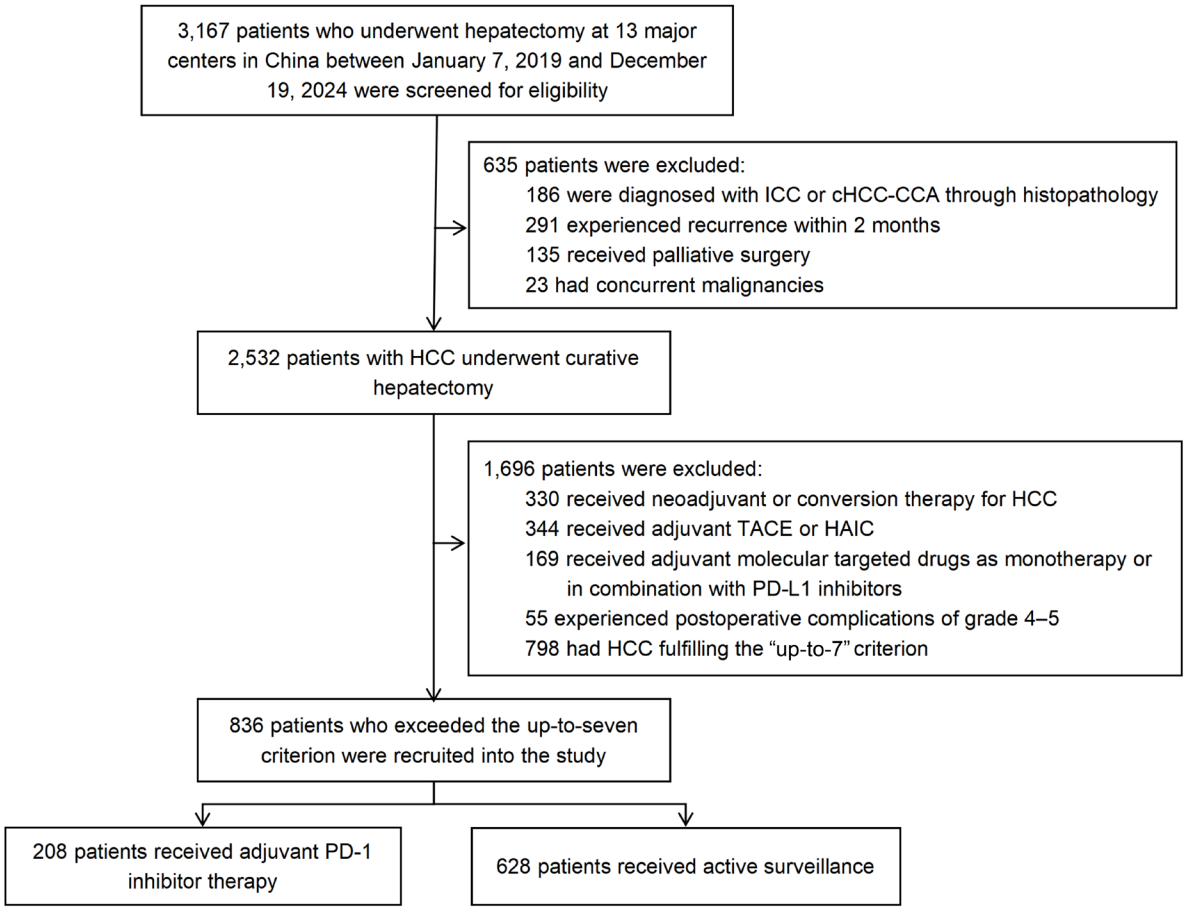


Fig. 1. Flow diagram of patient selection. cHCC-CCA, combined hepatocellular-cholangiocarcinoma; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; PD-L1, programmed cell death ligand 1; TACE, transarterial chemoembolization.

tumor size, tumor number, macrovascular invasion, microvascular invasion, Edmondson–Steiner grade, and surgical margin. Propensity scores were derived from the model, and the two groups were matched 1:1 using nearest-neighbor matching without replacement and a caliper width of 0.2. Covariate imbalance after matching was considered negligible when the standardized mean difference (SMD) was < 0.1.

Kaplan–Meier analyses of recurrence-free and overall survival were performed in the matched subgroups, and between-group differences were assessed using the log-rank test. Variables associated with survival at $P < 0.05$ in univariable Cox regression were included in multivariable Cox proportional hazards models. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Association analyses were also repeated in patients whose adjuvant therapy included antibodies recommended as first-line treatments for advanced HCC—tislelizumab, sintilimab, or camrelizumab.[23–25]

Several sensitivity analyses were performed to assess the robustness of the results. First, confounders were identified using the DAG, and stabilized inverse probability of treatment weighting (sIPTW) based on these confounders was applied to balance baseline differences between groups. Second, to assess potential censoring bias, patients were retained in the risk set until the end of follow-up rather than censored during follow-up. Third, three multivariable regression models adjusted for different sets of potential confounders identified from the literature and clinical practice guidelines. Model 1 adjusted for age and sex. Model 2 adjusted for variables associated with recurrence in univariable analysis ($P < 0.05$) or producing a ≥ 10% change in the effect estimate: age, sex, alpha-fetoprotein, tumor size, number of tumors, macrovascular and microvascular invasion, and Edmondson–Steiner grade. Model 3 adjusted for the Model 2 variables plus HBsAg status, Eastern Cooperative Oncology Group Performance Status, albumin–bilirubin grade, Child-Pugh class, liver cirrhosis, MASLD, and resection margin. Fourth, coarsened exact matching was performed to improve covariate balance through interval grouping; covariates were coarsened appropriately, and the closest possible matches were identified between the adjuvant therapy and active surveillance groups. Fifth, survival analyses were performed using a 12-month landmark after T0.

Results

Patient characteristics

Of 3,167 patients prospectively screened across 13 medical centers in China, 836 were enrolled: 97 (11.6%) received adjuvant PD-1 inhibitors alone, 111 (13.3%) received adjuvant PD-1 inhibitors combined with molecularly targeted agents, and 628 (75.1%) underwent active surveillance (Fig. 1). The distribution of specific treatment regimens is pro-

vided in Supplementary Table 3. Most patients were male (721, 86.2%) and had chronic hepatitis B virus infection (664, 79.4%); mean age was 53.5 ± 11.8 years (Table 1).

Before propensity score matching, several baseline characteristics differed between the adjuvant therapy and active surveillance groups, with SMDs > 0.1. These imbalances were minimized after matching (Table 1, Supplementary Table 5, and Supplementary Fig. 2), as also shown in the probability density plots (Supplementary Fig. 3).

Median follow-up for the entire cohort was 32.7 months (IQR, 20.9–47.5). Median duration of adjuvant therapy was 7.3 months (IQR, 5.3–12.0), and the median interval from hepatectomy to initiation of adjuvant therapy was 38 days (IQR, 28–47).

Recurrence-free survival

During follow-up, recurrence occurred in 106 patients (51.0%) in the adjuvant therapy group and 403 (64.2%) in the active surveillance group. Among patients with recurrence, the proportions with early (≤ 2 years) and late (> 2 years) recurrence were similar between groups. More than two-thirds of recurrences were intrahepatic (Supplementary Table 6). Liver function at recurrence, assessed using the albumin–bilirubin score, was similar between groups (Supplementary Fig. 4).

Before propensity score matching, median recurrence-free survival was 27.0 months (95% CI, 21.0–33.1) in the adjuvant therapy group and 18.9 months (95% CI, 15.5–22.4) in the active surveillance group. In the matched subgroups, the corresponding medians were 28.0 months (95% CI, 21.7–34.3) and 14.4 months (95% CI, 10.7–18.1). Recurrence-free survival rates at 12, 24, and 36 months were 70.2%, 55.1%, and 42.5%, respectively, in the adjuvant therapy group and 56.2%, 36.6%, and 27.1%, respectively, in the active surveillance group (Supplementary Table 7).

Before propensity score matching, adjuvant therapy was associated with longer recurrence-free survival (HR, 0.72; 95% CI, 0.59–0.88; P = 0.002; Fig. 2A). This association persisted in the propensity score-matched subgroups (HR, 0.58; 95% CI, 0.45–0.74; P < 0.001; Fig. 2B), the alternative Td analysis (HR, 0.73; 95% CI, 0.60–0.90; P = 0.003; Supplementary Fig. 5A), the cohort without censoring (HR, 0.71; 95% CI, 0.57–0.88; P = 0.002; Figs. 3 and 4A), the coarsened exact matching cohort (HR, 0.74; 95% CI, 0.56–0.97; P = 0.027; Figs. 3 and 4B), and the sIPTW cohort (HR, 0.67; 95% CI, 0.53–0.85; P = 0.002; Figs. 3 and 4C). The association was also consistent in sensitivity analyses using the unweighted Cox model for the entire cohort, the unadjusted Cox model for the propensity score-matched subgroups, and the multivariable-adjusted Cox models described in Materials and methods (Models 1–3; Fig. 3).

Within 12 months after hepatectomy, adjuvant therapy was associated with longer recurrence-free survival (HR, 0.65; 95% CI, 0.51–0.84; P = 0.002; Figs. 3 and 5A), whereas no significant between-group difference was observed beyond 12 months (Figs. 3 and 5A). Similar patterns were observed in the propensity score-matched subgroups (Fig. 5B).

In the entire cohort, recurrence-free survival did not differ significantly among patients receiving different PD-1 inhibitors (Supplementary Fig. 6A) or between patients receiving PD-1 inhibitor monotherapy and those receiving PD-1 inhibitors combined with molecularly targeted agents (HR, 0.99; 95% CI, 0.68–1.45; P = 0.971; Supplementary Fig. 7A). Compared separately with active surveillance, both adjuvant PD-1 monotherapy and PD-1 inhibitor plus targeted-agent combination therapy were associated with longer recurrence-free survival: HR, 0.72 (95% CI, 0.56–0.93; P = 0.028; Supplementary Fig. 8A) for monotherapy and HR, 0.72 (95% CI, 0.56–0.92; P = 0.020; Supplementary Fig. 8B) for combination therapy.

After recurrence, most patients received interventional therapy, immune checkpoint inhibitors, and/or targeted therapy; some underwent repeat curative resection or ablation (Supplementary Table 8). The frequencies of these treatments did not differ significantly between groups (Supplementary Table 8).

Overall survival

During follow-up, 50 patients (24.0%) in the adjuvant therapy group and 205 (32.6%) in the active surveillance group died. Before propensity score matching, median overall survival was not reached in the adjuvant therapy group (95% CI, 48.0 months to not evaluable) and was 62.7 months (95% CI, 50.4 months to not evaluable) in the active surveillance group. After matching, median overall survival was not reached in the adjuvant therapy group (95% CI, 48.0 months to not evaluable) and was 45.0 months (95% CI, 37.8–52.1) in the active surveillance group. Overall survival rates at 12, 24, and 36 months were 92.4%, 81.9%, and 71.4%, respectively, in the adjuvant therapy group and 85.8%, 72.2%, and 59.5%, respectively, in the active surveillance group (Supplementary Table 9).

Before propensity score matching, adjuvant therapy was associated with longer overall survival (HR, 0.71; 95% CI, 0.54–0.94; P = 0.031; Fig. 2C). This association persisted in the propensity score-matched subgroups (HR, 0.63; 95% CI, 0.45–0.89; P = 0.011; Fig. 2D), the alternative Td analysis (HR, 0.73; 95% CI, 0.55–0.97; P = 0.032; Supplementary Fig. 5B), the cohort without censoring (HR, 0.76; 95% CI, 0.56–0.97; P = 0.046; Fig. 4D and Supplementary Fig. 9), the coarsened exact matching cohort (HR, 0.61; 95% CI, 0.40–0.93; P = 0.019; Fig. 4E and Supplementary Fig. 9), and the sIPTW cohort (HR, 0.55; 95% CI, 0.39–0.77; P = 0.027; Fig. 4F and Supplementary Fig. 9). The association was also consistent in sensitivity analyses using Models 1–3 (Supplementary Fig. 9).

At the 12-month landmark, adjuvant therapy was associated with longer overall survival within 12 months after hepatectomy (HR, 0.48; 95% CI, 0.31–0.75; P = 0.008; Fig. 5C), whereas no significant between-group difference was observed beyond 12 months (Fig. 5C). Similar patterns were observed in the propensity score-matched subgroups (Fig. 5D).

In the entire cohort, overall survival did not differ significantly among patients receiving different PD-1 inhibitors (Supplementary Fig. 6B) or between patients receiving PD-1 inhibitor monotherapy and those receiving PD-1 inhibitors combined with molecularly targeted agents (HR, 1.14; 95% CI, 0.66–1.99; P = 0.635; Supplementary Fig. 7B). In separate comparisons with active surveillance, both treatment strategies showed associations favoring longer overall survival: HR, 0.76 (95% CI, 0.52–1.10; P = 0.191; Supplementary Fig. 8C) for PD-1 monotherapy and HR, 0.67 (95% CI, 0.47–0.95; P = 0.045; Supplementary Fig. 8D) for combination therapy.

Subgroup analyses of overall and recurrence-free survival

Adjuvant therapy was associated with longer recurrence-free and overall survival in most subgroups (Fig. 3 and Supplementary Fig. 9). A significantly lower hazard of recurrence was observed among patients aged ≥ 65 years, male pa-

Table 1. Comparison of clinicodemographic characteristics between patients who received adjuvant therapy or active surveillance after curative hepatectomy, before and after propensity score matching

Variable	Entire cohort			Propensity score-matched subsets		
	Active surveillance (n = 628)	Adjuvant therapy (n = 208)	SMD	Active surveillance (n = 200)	Adjuvant therapy (n = 200)	SMD
Age, years	54.3 ± 11.9	51.2 ± 11.3	0.271	52.5 ± 12.4	51.8 ± 10.9	0.058
Sex			0.098			0.014
Female	81 (12.9)	34 (16.3)		29 (14.5)	32 (16.0)	
Male	547 (87.1)	174 (83.7)		171 (85.5)	168 (84.0)	
HBsAg			0.127			0.013
Negative	137 (21.8)	35 (16.8)		42 (21.0)	35 (17.5)	
Positive	491 (78.2)	173 (83.2)		158 (79.0)	165 (82.5)	
Antiviral therapy	546 (86.9)	177 (85.1)	0.048	174 (87.0)	172 (86.0)	0.030
Alpha-fetoprotein, ng/mL			0.109			0.030
< 400	366 (58.3)	110 (52.9)		106 (53.0)	109 (54.5)	
≥ 400	262 (41.7)	98 (47.1)		94 (47.0)	91 (45.5)	
ECOG PS			0.075			0.063
0	520 (82.8)	166 (79.8)		158 (79.0)	160 (80.0)	
1	108 (17.2)	42 (20.2)		42 (21.0)	40 (20.0)	
ALBI grade			0.236			0.030
1	210 (33.4)	94 (45.2)		90 (45.0)	87 (43.5)	
2	409 (65.1)	110 (52.9)		105 (52.5)	109 (54.5)	
3	9 (1.4)	4 (1.9)		5 (2.5)	4 (2.0)	
Child-Pugh class			0.008			< 0.001
A	575 (91.6)	190 (91.3)		183 (91.5)	183 (91.5)	
B	53 (8.4)	18 (8.7)		17 (8.5)	17 (8.5)	
Liver cirrhosis			0.186			0.011
Absent	139 (22.1)	63 (30.3)		59 (29.5)	58 (29.0)	
Present	489 (77.9)	145 (69.7)		141 (70.5)	142 (71.0)	
MASLD			0.094			0.013
Absent	538 (85.7)	171 (82.2)		167 (83.5)	166 (83.0)	
Present	90 (14.3)	37 (17.8)		33 (16.5)	34 (17.0)	
BCLC stage			0.147			0.085
0/A	356 (56.7)	103 (49.5)		92 (46.0)	101 (50.5)	
B	104 (16.6)	38 (18.3)		50 (25.0)	36 (18.0)	
C	168 (26.8)	67 (32.2)		58 (29.0)	63 (31.5)	
Tumor size, cm	9.9 ± 3.4	9.9 ± 3.3	0.003	9.8 ± 3.4	9.9 ± 3.2	0.035
Number of tumors			0.219			0.038
1	490 (78.0)	141 (67.8)		137 (68.5)	138 (69.0)	
2	67 (10.7)	31 (14.9)		24 (12.0)	28 (14.0)	
≥ 3	71 (11.3)	36 (17.3)		39 (19.5)	34 (17.0)	
Macrovascular invasion			0.074			0.062
Absent	505 (80.4)	161 (77.4)		161 (80.5)	156 (78.0)	
Present	123 (19.6)	47 (22.6)		39 (19.5)	44 (22.0)	
Microvascular invasion			0.225			0.099

(continued)

Table 1. *(continued)*

Variable	Entire cohort			Propensity score-matched subsets		
	Active surveillance (n = 628)	Adjuvant therapy (n = 208)	SMD	Active surveillance (n = 200)	Adjuvant therapy (n = 200)	SMD
Absent	339 (54.0)	89 (42.8)		99 (49.5)	89 (44.5)	
Present	289 (46.0)	119 (57.2)		101 (50.5)	111 (55.5)	
Edmondson–Steiner grade			0.060			0.040
I–II	363 (57.8)	114 (54.8)		108 (54.0)	112 (56.0)	
III–IV	265 (42.2)	94 (45.2)		92 (46.0)	88 (44.0)	
Resection margin, cm			0.418			0.050
< 1	423 (67.4)	98 (47.1)		92 (46.0)	97 (48.5)	
≥ 1	205 (32.6)	110 (52.9)		108 (54.0)	103 (51.5)	

Values are mean ± SD or n (%), unless otherwise noted. ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBsAg, hepatitis B surface antigen; MASLD, metabolic dysfunction-associated steatotic liver disease; SD, standard deviation; SMD, standardized mean difference.

tients, and patients with alpha-fetoprotein ≥ 400 ng/mL, cirrhosis, non-MASLD, or Barcelona Clinic Liver Cancer (BCLC) stage B or C disease (Fig. 3). A trend toward longer overall survival was observed with adjuvant therapy (Supplementary Fig. 9).

These findings were consistent after propensity score matching (Supplementary Figs. 10–11) and coarsened exact matching (Supplementary Figs. 12–13).

First-line immunotherapies in the adjuvant setting

We compared survival between patients who received tislelizumab, sintilimab, or camrelizumab, either alone or combined with molecularly targeted agents, and patients who underwent active surveillance (Supplementary Table 10). Median recurrence-free survival in the adjuvant therapy group was 28.0 months (95% CI, 23.0–33.0), and adjuvant therapy was associated with longer recurrence-free survival than active surveillance (HR, 0.73; 95% CI, 0.59–0.90; P = 0.006; Fig. 3 and Supplementary Fig. 14A). Median overall survival was not reached in the adjuvant therapy group (95% CI, 48.0 months to not evaluable), and adjuvant therapy was also associated with longer overall survival (HR, 0.72; 95% CI, 0.54–0.97; P = 0.049; Supplementary Figs. 9 and 14B). Similar findings were obtained in the propensity score-matched subsets (Supplementary Fig. 14C–D).

Independent factors associated with survival

Univariable and multivariable Cox regression analyses in the overall cohort showed that adjuvant PD-1 inhibitors, with or without molecularly targeted agents, were independently associated with lower hazards of recurrence (HR, 0.61; 95% CI, 0.48–0.76; P < 0.001) and death (HR, 0.66; 95% CI, 0.48–0.90; P = 0.008; Supplementary Table 11). After propensity score matching, adjuvant therapy remained associated with lower hazards of recurrence (HR, 0.58; 95% CI, 0.45–0.74; P < 0.001) and death (HR, 0.64; 95% CI, 0.44–0.91; P = 0.013; Supplementary Table 12). Before and after matching, microvascular invasion was among the strongest factors associated with higher risks of recurrence and mortality (Supplementary Tables 11–12).

Toxicity of adjuvant therapy

Among 208 patients who received adjuvant therapy, 160 (76.9%) experienced treatment-related adverse events of any grade, including 61 (29.3%) with grade 3–4 events (Supplementary Table 13). The most frequent grade 3–4 events were hand–foot skin reaction (7.2%), elevated alanine aminotransferase (5.8%), and elevated aspartate aminotransferase (5.3%). Any-grade immune-related adverse events (irAEs) occurred in 61.1% of patients, and grade 3–4 irAEs occurred in 21.1%. The incidence of irAEs was similar between patients receiving PD-1 inhibitor monotherapy and combination therapy. Adverse events led to treatment discontinuation in 9.6% of patients, with grade 3–4 toxicities accounting for most discontinuations (8.7%).

Discussion

This large multicenter cohort study, based on prospectively collected data and analyzed using a target trial emulation framework, suggests that adjuvant PD-1 therapy, alone or combined with molecularly targeted agents, is associated with longer recurrence-free and overall survival after curative hepatectomy in patients with HCC exceeding the "up-to-7" criterion. Adjuvant therapy also showed an acceptable safety profile. The association with lower recurrence risk appeared more pronounced during the first 12 months after surgery, whereas the additional effect of molecularly targeted agents remains uncertain.

Our findings are consistent with studies suggesting that adjuvant PD-1 inhibitors may improve prognosis,[6,8,26] including phase II clinical trials.[5,27] Our previous work also suggested that patients with HCC containing tertiary lymphoid structures may be more likely to benefit.[28] One proposed mechanism is that PD-1 inhibitors activate antitumor immune responses and promote recruitment of $CD8^+$T cells to tumors.[29] In contrast, the IMbrave050 trial did not show a significant recurrence benefit for combined PD-L1 and angiogenesis inhibition among patients whose tumors had PD-L1 expression > 1%.[9] Differences between PD-1 and PD-L1 inhibitors may partly reflect differences in their mechanisms of action and patterns of target expression.[10] In addition, it remains unclear whether micrometastases or circulating tumor cells remaining after resection express sufficient PD-L1 for effective targeting. These considerations may help explain why median recurrence-free survival in our entire adjuvant PD-1 inhibitor group (27.0 months; 95% CI, 21.0–33.1) was longer than that reported for patients exceeding the "up-to-7" criterion in IMbrave050 (16.9 months; 95% CI, 14.7–27.6).

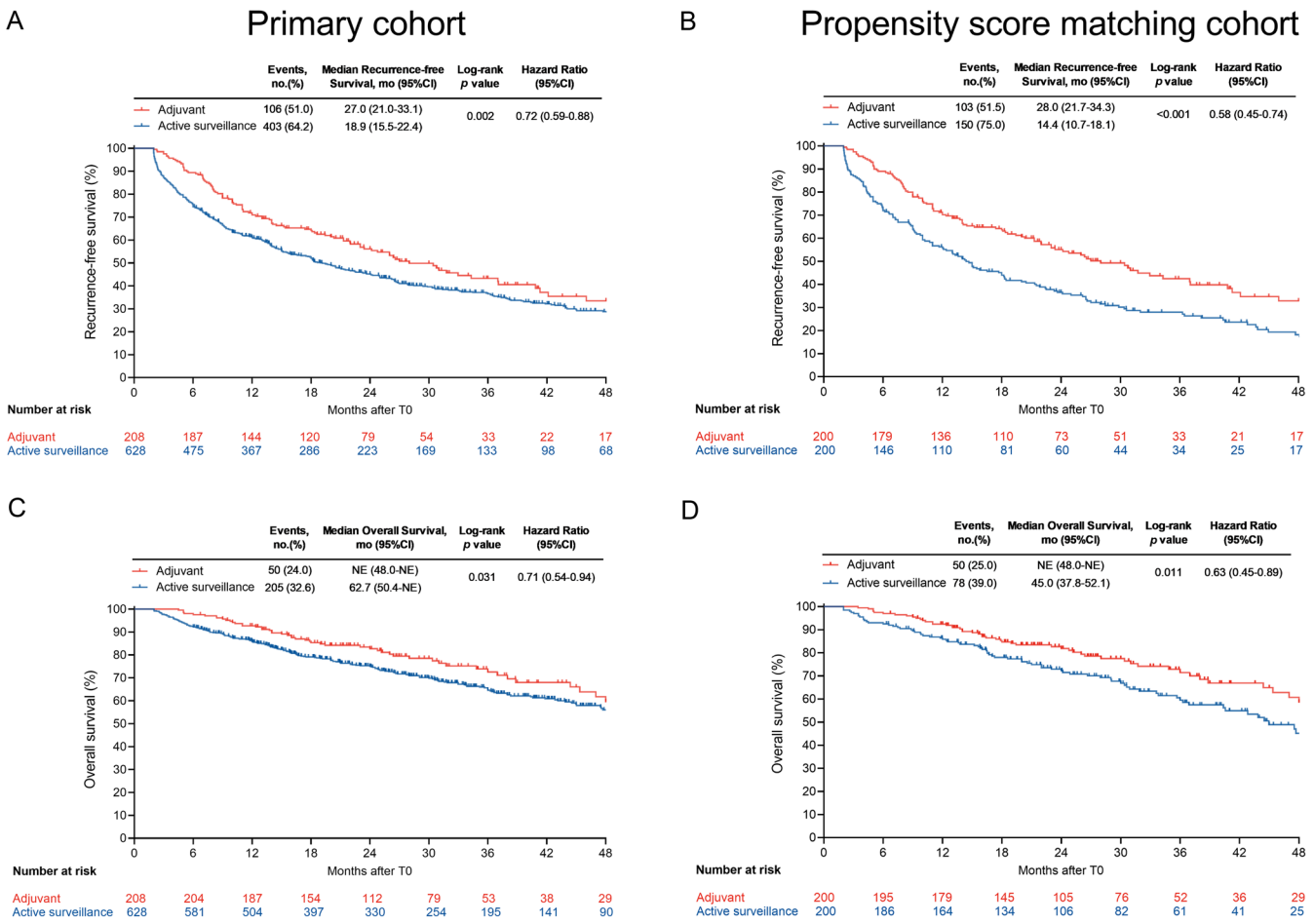


Fig. 2. Prognoses of patients with hepatocellular carcinoma exceeding the "up-to-7" criterion who received adjuvant PD-1 therapy or active surveillance. (A, B) Recurrence-free survival in (A) the entire cohort and (B) the propensity score-matched subsets. (C, D) Overall survival in (C) the entire cohort and (D) the propensity score-matched subsets. CI, confidence interval; HR, hazard ratio; PD-1, programmed cell death protein 1.

Notably, the phase III KEYNOTE-937 trial[30] showed no significant recurrence-free survival benefit with adjuvant pembrolizumab in an unselected high-risk HCC population, potentially reflecting the large proportion of early-stage patients and broad definition of recurrence risk. In contrast, perioperative camrelizumab plus rivoceranib in the CARES-009 trial[31] showed favorable results in resectable intermediate- to high-risk HCC; 55% of patients had a single lesion and 47% had BCLC stage B/C disease, more closely resembling the high-risk population encountered in clinical practice. These divergent results suggest that patient selection and treatment strategy may influence observed efficacy. Our study focused on patients exceeding the "up-to-7" criterion and found that adjuvant PD-1-based therapy was associated with longer survival in this high-risk population.

These divergent findings may also reflect the influence of clinical factors on HCC recurrence, including tumor number and size, tumor differentiation grade, macrovascular or microvascular invasion, and liver function.[32] In IMbrave050, patients with only one high-risk recurrence factor did not appear to benefit from adjuvant therapy.[9] Future studies should clarify which patients are most likely to benefit from adjuvant immune checkpoint inhibitor therapy and the mechanisms underlying any benefit. The "up-to-7" criterion integrates tumor size and number, and our findings suggest that patients exceeding this threshold may represent a population in whom adjuvant PD-1 therapy warrants further investigation.

Data from IMbrave050 suggest that the recurrence-free survival benefit began to wane after 1 year of treatment.[9] Consistent with this observation, our 12-month landmark analysis suggested that the association between adjuvant PD-1 inhibitor therapy and lower recurrence risk was more pronounced during the first 12 months after surgery. Similar findings have been reported in retrospective studies.[33,34] Potential explanations for a time-limited treatment effect include immune escape of minimal residual disease, insufficient durable antitumor immune memory, and proliferation of resistant tumor clones. These findings highlight the need to continue developing and optimizing adjuvant strategies to reduce recurrence.

In our study, survival outcomes did not differ significantly by PD-1 inhibitor type, including tislelizumab, sintilimab, camrelizumab, and other agents. Because head-to-head trials are lacking, differences in efficacy among these inhibitors remain uncertain.[35] Pending comparative data, treatment selection may therefore depend on patient characteristics, comorbidities, drug accessibility, and cost.

Additional subgroup analyses showed that both adjuvant PD-1 inhibitor monotherapy and PD-1 inhibitors combined

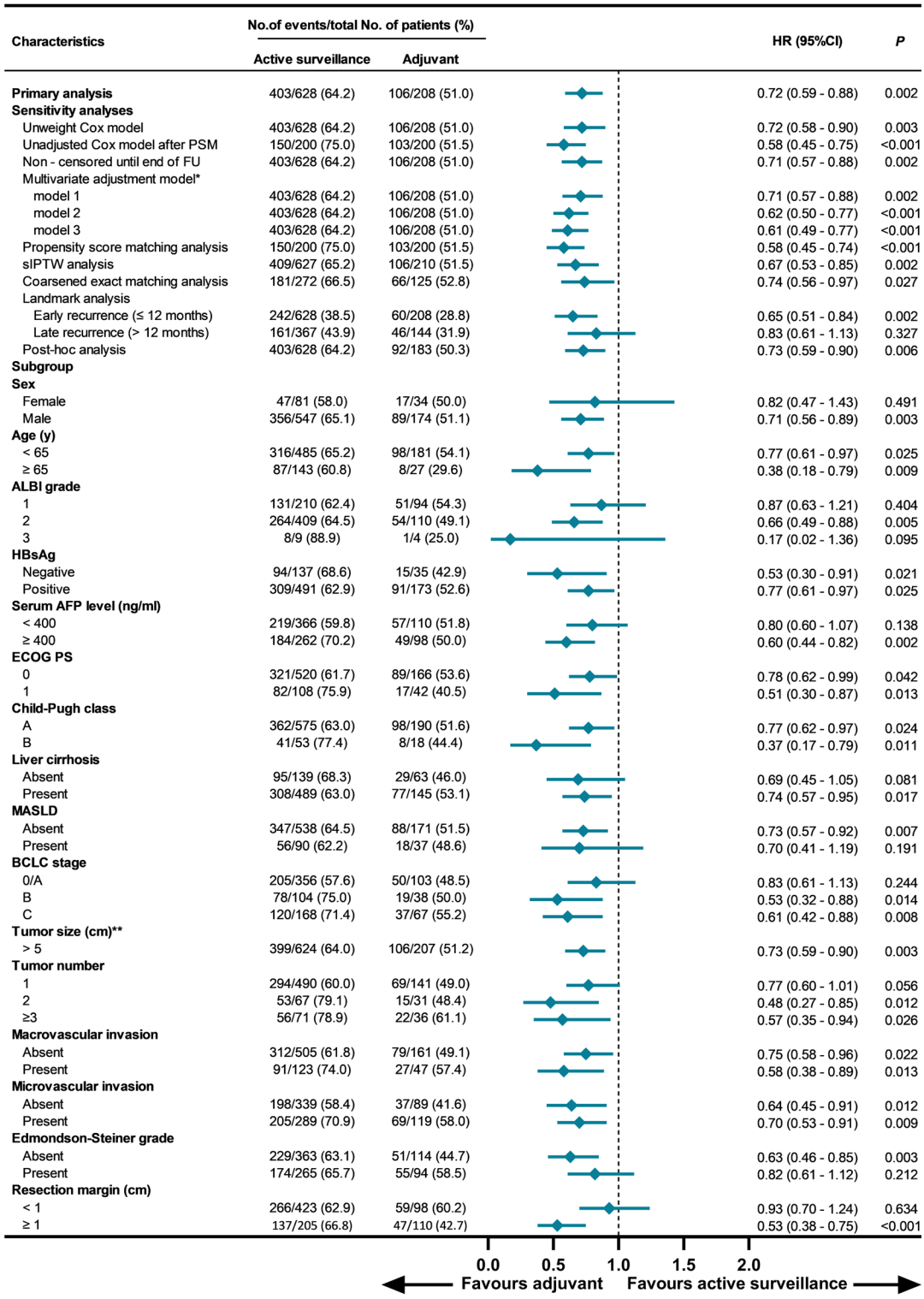


Fig. 3. Sensitivity and subgroup analyses of recurrence-free survival. *Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, alpha-fetoprotein, number and size of tumors, macrovascular and microvascular invasion, and Edmondson–Steiner grade. Model 3 adjusted for the same variables as Model 2, as well as HBsAg, Eastern Cooperative Oncology Group Performance Status, albumin–bilirubin grade, Child-Pugh class, liver cirrhosis, metabolic dysfunction-associated steatotic liver disease, and resection margin. **Subgroup analysis was not performed because of the small sample (n = 5) and small number of patients with tumors < 5 cm. AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer staging system; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FU, follow-up; HBsAg, hepatitis B surface antigen; HR, hazard ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; PSM, propensity score matching; sIPTW, stabilized inverse probability of treatment weighting.

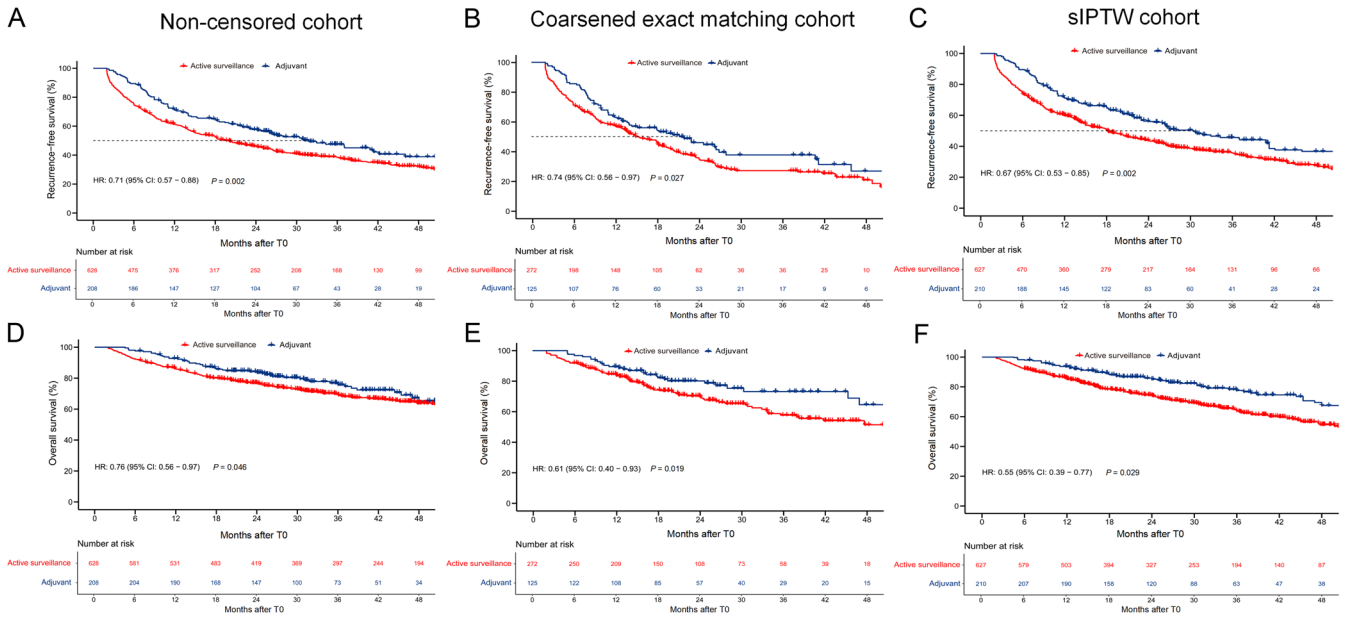


Fig. 4. Sensitivity analyses of (A–C) recurrence-free survival and (D–F) overall survival in patients who received adjuvant therapy or active surveillance. (A, D) Noncensored cohort. (B, E) Coarsened exact matching cohort. (C, F) Stabilized inverse probability of treatment weighting cohort. CI, confidence interval; HR, hazard ratio; sIPTW, stabilized inverse probability of treatment weighting.

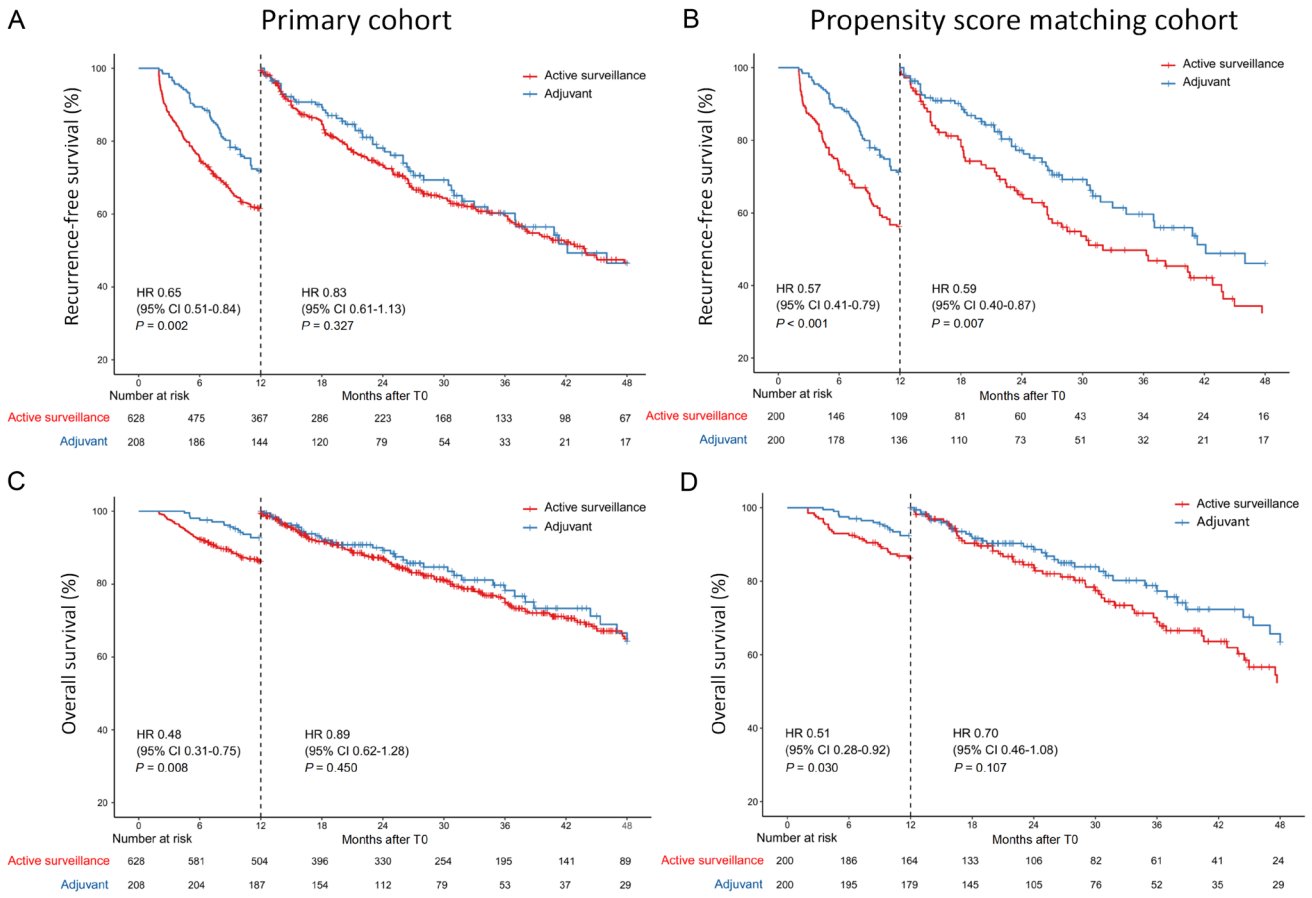


Fig. 5. Landmark survival analysis at a cutoff of 12 months. (A, B) Recurrence-free survival in (A) the entire cohort and (B) the propensity score-matched subsets. (C, D) Overall survival in (C) the entire cohort and (D) the propensity score-matched subsets. CI, confidence interval; HR, hazard ratio.

with molecularly targeted agents were associated with longer recurrence-free survival than active surveillance. For overall survival, statistical significance was observed only in the combination group, whereas PD-1 monotherapy showed a favorable but nonsignificant trend. However, direct comparison of monotherapy and combination regimens showed no significant difference in recurrence-free or overall survival. The differing levels of statistical significance may reflect individual recurrence risk, unmeasured confounders such as postoperative recovery, psychological stress, and financial capacity, and limited statistical power due to the small sizes of the two treatment subgroups. Therefore, the nominally significant overall survival association in the combination group cannot be attributed solely to the addition of molecularly targeted agents, and the value of routine combination therapy requires further investigation.[36]

Our findings should be interpreted in light of several limitations. First, treatment allocation was based on patient or family preference rather than randomization, which may have introduced selection bias. Second, the diversity of treatment regimens and pooling of monotherapy and combination therapy may have introduced heterogeneity. Third, unmeasured confounders, including postoperative recovery, emotional stress, and financial capacity, may have influenced treatment allocation and outcomes, limiting causal interpretation. Fourth, overall survival data remain immature because of the relatively short follow-up, and longer observation with additional mortality events is needed to assess the durability of the observed associations. In addition, most patients had chronic hepatitis B virus infection, as is common in many Asian HCC populations; further evaluation is needed in patients with HCC of other etiologies. Finally, variation in follow-up schedules and routine clinical management across centers may have introduced additional bias. These findings require confirmation in larger studies with longer follow-up, preferably randomized controlled trials.

Conclusions

Our findings suggest that adjuvant PD-1 inhibitors, with or without molecularly targeted agents, are associated with longer recurrence-free and overall survival and acceptable safety after curative resection in patients with HCC exceeding the "up-to-7" criterion. Further studies are needed to identify the patient populations most likely to benefit and to determine the optimal adjuvant regimen.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JCTH.2026.00283.

Funding

This work was supported by the Natural Science Foundation of Guangxi (2025GXNSFBA069027), Guangxi Science and Technology Program (AD25069077), First-class Discipline Innovation-driven Talent Program of Guangxi Medical University, Key Laboratory of Biological Molecular Medicine Research (Guangxi Medical University), Education Department of Guangxi Zhuang Autonomous Region (GXSWFZ202301), Guangxi Undergraduate Training Program for Innovation and Entrepreneurship (S202510598221), Key Laboratory of Human Development and Disease Research (Guangxi Medical University), and Education Department of Guangxi Zhuang Autonomous Region (RTFY202501).

Conflict of interest

JHZ is an Editorial Board Member of the *Journal of Clinical and Translational Hepatology* since 2020. The authors have no other conflicts of interest related to this publication.

Author contributions

Study conception (JHZ); data collection (JYS, SPL, XFD, XLX, SCC, JJO, KC, ZCL, ZS, FQY, WHH, NP, PSW, BBL, HS, JRL, MLH, WTL, WTC, DLY, ZHH, LPL); data analysis (YLM, RRH); drafting the manuscript (JYS, TXY, PPG, ZL, ML, JHZ); and critical revision of the manuscript (XBZ, JHZ, LM). All authors reviewed and approved the final manuscript, had full access to the study data, and share responsibility for the decision to submit it for publication.

Ethical statement

This clinical study was conducted in accordance with the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained from each participant before enrollment, and consent documents were archived. The study protocol received ethical approval from the ethics committees of the 13 participating medical centers in China, with Guangxi Medical University Cancer Hospital in Nanning, China serving as the lead site (LW2021103) and registered at ClinicalTrials.gov (NCT05221398).

Data sharing statement

All available data are included in this article. Additional original data are available from the corresponding authors in accordance with privacy and ethical restrictions.

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