RESEARCH ARTICLE

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Efficacy of Adjuvant Transarterial Chemoembolization Combined Antiviral Therapy for HBV-Related HCC with MVI after Hepatic Resection: A Multicenter Study

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Abstract

Background: Efficacy of transarterial chemoembolization (TACE) combined antiviral therapy (AVT) on long-term outcome in hepatitis B virus-related HCC with microvascular invasion (MVI) after hepatic resection is unclear. **Methods:** A multicenter retrospective study was conducted. All patients were divided into four groups according to postoperative adjuvant therapy (control group, AVT group, TACE group, and combined group). The overall survival (OS) and recurrence-free survival (RFS) were analyzed. **Results:** A total of 1090 patients were enrolled in this study, including control group (n=319), TACE group (n=152), AVT group (n=335) and combined group (n=284). Multivariate Cox analysis showed that postoperative adjuvant AVT and TACE were the independent protective factors for OS and RFS. The median OS among the control group, TACE group, AVT group, and the combined group were 16.44, 18.36 months, 38.88 months, and 48.24 months respectively($p<0.01$). The median RFS among 4 group were 4.68, 5.40 months, 8.64 months and 10.32 months respectively($p<0.01$). **Conclusions:** Postoperative adjuvant TACE and AVT were the independent protective factors associated with mortality and tumor recurrence in HBV-related HCC with MVI after resection. This combined treatment strategy may provide useful clinical significance in the prevention of tumor recurrence in these patients.

Keywords: Hepatocellular carcinoma- curative hepatectomy- long-term outcome- transarterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) accounts for more than 80% of all primary liver cancers and is one of the most common malignancies worldwide(Forner et al., 2018; Sung et al., 2021). Hepatic resection (HR) has been used as the most common acceptable radical therapy for HCC(Portolani et al., 2006). However, the long-term outcome is unsatisfied, primarily attributed to high rates of tumor recurrence (Tandon and Garcia-Tsao, 2009). Hepatitis B virus (HBV) and microvascular invasion (MVI) have been reported to be two well-known independent prognostic factors (Lim et al., 2011; Li et al., 2018; Zhang et al., 2018).

Postoperative antiviral therapy (AVT) and transarterial chemoembolization (TACE) are frequent adjuvant therapy to prevent HCC recurrence. Routine postoperative AVT has been reached consensus on guidelines at present (European Association for the Study of the Liver. Electronic address and European Association for the Study of the, 2018; Zhou et al., 2018). Several studies and meta-analyses provide updated evidence to support adjuvant TACE as a possible treatment to improve the long-term oncological prognosis for patients undergoing curative resection for HCC, especially in those patients with MVI (Wei et al., 2018; Chen et al., 2019; Wang et al., 2019; Ahmad et al.,2019).

There are two studies that showed the combination of postoperative TACE and AVT may be more effective than isolated TACE or AVT treatment in reducing the recurrence in patients with HBV-related HCC after HR, but there is not provide sufficient evidence due to about 100 patients were enrolled (Yan et al., 2013; Zhu et al., 2018). Therefore, the long-term outcome of this treatment strategy still needs more data supporting, especially for HBV-related HCC patients with MVI.

To address this issue, we conducted a large multicenter study to investigate the long-term outcome of the treatment of postoperative adjuvant TACE combined AVT for HBV-related HCC with MVI after hepatic resection.

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Materials and Methods

Patients and methods

Patients

This study was conducted to the ethical guideline of the 1975 Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Mengchao Hepatobiliary Hospital of Fujian Medical University (No.: 2021_117_01). The data of patients who underwent curative hepatectomy of HCC between January 2011 and December 2015 were collected from three Chinese hepatobiliary medical centers, including Mengchao Hepatobiliary Hospital of Fujian Medical University, The First Affiliated Hospital of Fujian Medical University, and Eastern Hepatobiliary Surgery Hospital. The inclusion criteria were: (1) HCC with MVI was confirmed by histopathological examination; (2) patients tested positive for hepatitis B surface antigen [HBsAg (+)] and negative for hepatitis C antibody; (3) receipt of R0 resection, referring to the complete removal of all visible tumor nodules during surgery and a microscopically negative surgical margin(Wang et al., 2010). The exclusion criteria were as follows: (1) patients who received underwent preoperative anticancer treatments; (2) palliative tumor resection; (3) had the history of other malignancies; (4) had incomplete clinical data and lost to follow-up within 1 month of surgery.

Clinicopathologic variables

Blood samples were obtained within 14 days before surgery for routine laboratory tests for liver function and blood cells, including total bilirubin, albumin, platelet count, HBV deoxyribonucleic acid (HBV-DNA) load, and a-fetoprotein (AFP). The albumin-bilirubin (ALBI) grade was calculated by the formula, 0.66 × log10 (bilirubin, μmol/L)-0.085 (albumin, g/l) (Johnson et al., 2015). According to previously described cut-off resulted in 2 grades: ALBI grade 1 (≤-2.63), grade 2 (>-2.63 to-1.39), and grade 3 (>-1.39). ALBI grade 2 and ALBI grade 3 were grouped due to the low sample size in the latter. Patient baseline characteristics included demographic information, surgical factors, laboratory parameters, and tumor characteristics. Tumor features were collected by postoperative pathological reports (Zhou et al., 2017).

Surgical Procedure

All surgeries were conducted with the same standard technique. Surgery was conducted through a bilateral subcostal incision. The abdominal cavity was carefully searched for extent of local disease and extrahepatic metastases. Pringle's maneuver was used to occlude the blood inflow of the liver with cycles of 15-20 minutes clamp time and 5 minutes unclamped time. Liver resection was carried out by a clamp-crushing method (Wang et al., 2010).

Postoperative adjuvant TACE

Postoperative adjuvant TACE was performed within 1-2 months after hepatectomy without recurrence. Catheterization was placed into the proper hepatic artery through the femoral artery using the seldinger technique, and chemotherapeutic agents including doxorubicin hydrochloride (10 mg), pharmorubicin (20-40 mg), or cisplatin (10-30 mg) were slowly injected through the catheter followed by an emulsion of lipiodol (2-10 mL). The lipiodol and dosage chemotherapeutic agents were determined by liver function and body surface area.

Postoperative adjuvant AVT

Postoperative adjuvant AVT was defined as continuously using at least one type of AVT drug for more than 3 months after hepatectomy within 3 months. The indications of AVT were mainly according to the contemporary guidelines for the management of patients with HBV infection. The nucleoside and nucleotide analogues were used for AVT in this study, including lamivudine (100 mg per day) adefovir (10 mg per day), and entecavir (0.5 mg per day).

Follow-up

Patients were followed up once every 3-4 months for the first 2 years after discharge from hospitals and every 4-6 months in subsequent years. Follow-up examinations were conducted using laboratory findings (AFP, liver function, and complete blood count), abdominal ultrasonography, and contrast-enhanced CT or magnetic resonance imaging (MRI) of abdomen.

The diagnosis and management of tumor recurrence were relied on the evidence of imaging findings according to the current guidelines (European Association for the Study of the Liver. Electronic address and European Association for the Study of the, 2018). Primary end-points were overall survival (OS) and recurrence-free survival (RFS). OS was defined as the interval between the date of surgery and the date of patient death or the date of last follow-up. RFS was the interval between the date of surgery and the date when tumor recurrence was diagnosed or the date of patient death or the date of last follow-up. The follow-up was censored on 31st October 2021.

Statistical Analysis

Continuous variables were redefined as categorical variables. Categorical data were expressed as a number (percentage, %) and compared using the chi-square test or Fisher's exact test. Survival curves including OS and RFS were drawn by the Kaplan-Meier method, and the difference between two groups was tested using the log-rank test. Risk factors associated with prognosis of HCC were identified by the forward method of the multivariate Cox regression model. All statistical analysis was performed with spss version 20 (SPSS, Inc., Chicago, IL, USA) and R version 4.1.1 (R Project, Vienna, Austria). $P<0.05$ in all cases was considered statistically significant.

Results

Demographic and baseline characteristics

During the study period, A total of 1,167 patients with HBV-related HCC with MVI who received curative hepatectomy were included. Seventy seven patients were excluded due to palliative tumor resection (n=15), preoperative antitumor therapy (n=16), history of other

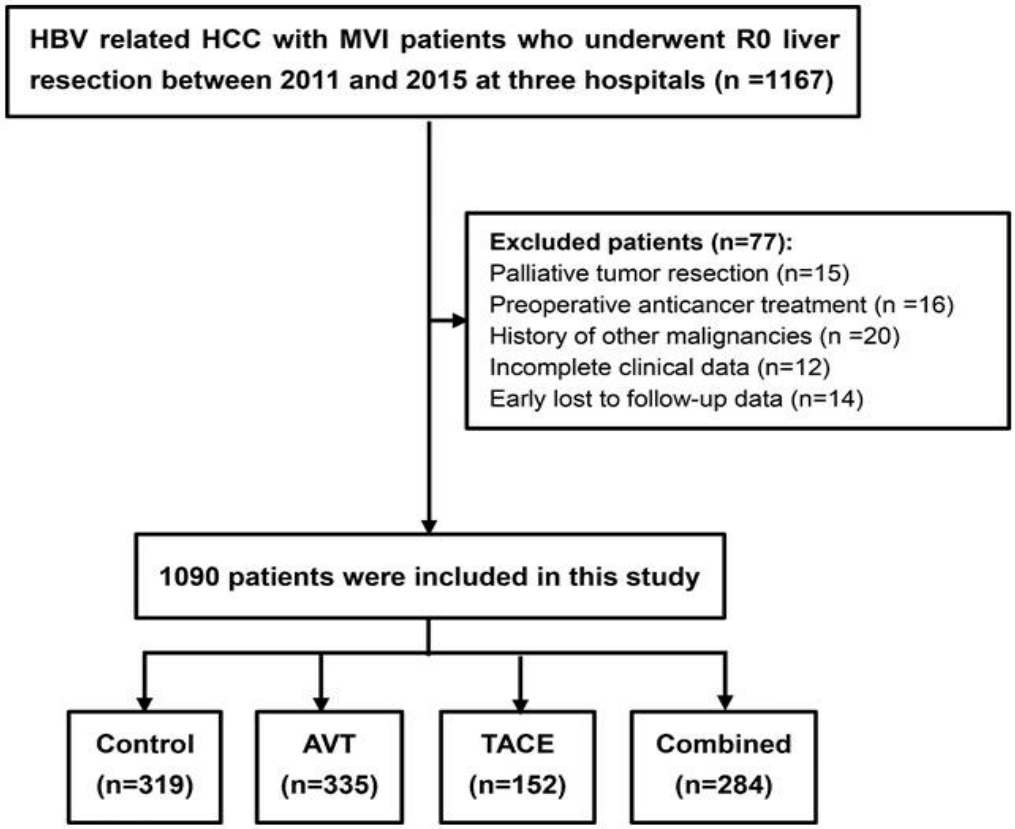

Figure 1. The Flow Chart of Selected Patients. Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MVI, microvascular invasion; AVT, antiviral therapy; TACE, transarterial chemoembolization

malignancies (n=20), incomplete clinical data (n=12), and the remainder not collected due to participants being discharged early and lost to follow-up (n=14). Finally, a total of 1,090 patients were enrolled in this study, including the control group (n=319), TACE group (n=152), AVT group (n=335), and combined group (n=284). The patient selection flow chart is shown in Figure 1. During the 5-year follow-up period, seven hundred and fifty-six patients died and six hundred and seventy-three patients relapsed.

As summarized in Table 1, Some clinicopathologic features such as AFP, blood transfusion, blood loss, liver cirrhosis, and tumor size were different among the four groups.

Risk factors associated with OS and RFS

Univariate and multivariate Cox analyses were performed to identify independent prognostic factors for OS and RFS (Table 2 and Table 3). Multivariate Cox analysis revealed that postoperative adjuvant AVT (HR=0.65, 95%CI=0.56-0.76, p<0.01) and postoperative adjuvant TACE (HR=0.75, 95%CI=0.64-0.87, p<0.01) were the independent protected factors associated with OS (Table 2). Postoperative adjuvant AVT (HR=0.75, 95%CI=0.66-0.86, p<0.01) and postoperative adjuvant TACE (HR=0.88, 95%CI=0.77-1.01, p=0.07) were the independent protected factor for tumor recurrence by multivariate analysis (Table 3).

Prognosis in different adjuvant therapy groups

The OS rates at 1, 3, 5-year were 54.9%, 37.3%, and 15.0% in control group, 60.0%, 34.2%, 21.6% in TACE group, 78.9%, 53.4%, 35.7% in AVT group, and 84.0%, 58.2%, 38.9% in combined group (Figure 2A, p<0.01). The median OS among control group, TACE group, AVT group, and combined group were 16.44 (95%CI=9.77-23.14) months, 18.36 (95%CI=12.00-24.72) months, 38.88 (95%CI=31.08-46.69) months and 48.24 (95%CI=31.08-46.69) months respectively (Figure 2A, p<0.01).

The recurrence-free survival rates at 1, 3, 5-year were 30.7%, 19.9%, and 6.8% in control group, 30.9%, `17.1%, 10.8% in TACE group, 44.1%, 25.3%, 17.6% in AVT group, and 44.5%, 24.1%, 18.7% in combined group (Figure 2B, p<0.01). The median RFS among control group, TACE group, AVT group, and combined group were 4.68 (95%CI=3.84-5,52) months, 5.40 (95%CI=4.05-6.75) months, 8.64 (95%CI=5.67-11.61) months and 10.32 (95%CI=8.30-12.34) months respectively (Figure 2B, p<0.01).

Discussion

Based on this study, we found that postoperative adjuvant TACE and AVT were prolonged OS and RFS for HBV-related HCC with MVI after liver resection (Figure 2). There are two studies showed that the treatment of postoperative TACE plus AVT may be more effective than isolated TACE or AVT treatment in reducing the

Table 1. Baseline Characteristics of Patients Underwent Curative Hepatectomy of HCC

Variables	Control group (n=319)	AVT group (n=335)	TACE group (n=152)	Combined group (n=284)	p-value
Age (years)					0.31
<50	170 (53.3)	174 (51.9)	87 (57.2)	167 (58.8)	
≥50	149 (46.7)	161 (48.1)	65 (42.8)	117 (41.2)	
Gender					0.28
Female	28 (8.8)	39 (11.6)	22 (14.5)	29 (10.2)	
Male	291 (91.2)	296 (88.4)	130 (85.5)	255 (89.8)	
HBV-DNA (IU/mL)					0.02
<2000	191 (59.9)	181 (54.0)	106 (69.7)	154 (54.2)	
≥2000	128 (40.2)	154 (46.0)	46 (30.3)	103 (45.8)	
HBeAg					<0.01
Negative	48 (16.3)	95 (29.0)	21 (13.8)	68 (25.4)	
Positive	267 (83.7)	238 (71.0)	131 (86.2)	212 (74.6)	
AFP (ng/mL)					<0.01
<400	145 (45.5)	181 (54.0)	77 (37.5)	156 (54.9)	
≥400	174 (54.5)	154 (46.0)	95 (62.5)	128 (45.1)	
WBC (109/L)					0.15
<4	54 (16.9)	70 (20.9)	20 (13.2)	45 (15.8)	
≥4	265 (83.1)	265 (79.1)	132 (86.8)	239 (84.2)	
PLT (109/L)					0.13
<100	39 (12.2)	57 (17.0)	18 (11.8)	50 (17.6)	
≥100	280 (87.8)	278 (83.0)	134 (88.2)	234 (82.4)	
ALB (g/L)					0.43
<35	16 (5.0)	10 (3.0)	4 (2.6)	9 (3.2)	
≥35	303 (95.0)	325 (97.0)	148 (97.4)	275 (96.8)	
TBIL (μmol/L)					0.33
<17.1	239 (74.9)	255 (6.1)	104 (68.4)	209 (73.6)	
≥17.1	80 (25.1)	80 (23.9)	48 (31.6)	75 (26.4)	
ALBI grade					0.05
Grade 1	224 (70.2)	260 (77.6)	119 (78.3)	224 (78.9)	
Grade 2	95 (29.8)	75 (22.4)	33 (21.7)	60 (21.1)	
Surgical margin (cm)					0.24
<1	50 (15.7)	63 (18.8)	18 (11.8)	51 (18.0)	
≥1	269 (84.3)	272 (81.2)	134 (88.2)	233 (82.0)	
Blood transfusion					<0.01
No	247 (77.4)	291 (86.9)	119 (78.3)	247 (87.0)	
Yes	72 (22.6)	44 (13.1)	33 (21.7)	37 (13.0)	
Blood loss (ml)					0.02
<800	261 (81.8)	298 (89.0)	127 (83.6)	253 (89.1)	
≥800	58 (18.2)	37 (11.0)	25 (16.4)	31 (10.9)	
Tumor size (cm)					<0.01
<5	84 (26.3)	144 (43.0)	28 (18.4)	118 (41.5)	
≥5	235 (73.7)	191 (57.0)	124 (81.6)	166 (58.5)	
Tumor number					0.07
Solitary	235 (73.7)	264 (78.8)	112 (73.7)	197 (69.4)	
Multiple	84 (26.3)	71 (21.2)	40 (26.3)	87 (30.6)	
Differentiation					0.19
I-II	10 (3.1)	22 (6.6)	6 (3.9)	12 (4.2)	
III-IV	309 (96.9)	313 (93.4)	146 (96.1)	272 (95.8)	

Table 1. Continued

Variables	Control group (n=319)	AVT group (n=335)	TACE group (n=152)	Combined group (n=284)	p-value
Tumor capsular					0.58
No	119 (37.3)	106 (31.6)	55 (36.2)	99 (34.9)	
Yes	200 (62.7)	229 (68.4)	97 (63.8)	185 (65.1)	
Liver cirrhosis					<0.01
F0 (0-4)	75 (23.5)	55 (16.4)	46 (30.3)	66 (23.2)	
F1 (5-6)	244 (76.5)	280 (83.6)	106 (69.7)	218 (76.8)	

Abbreviations: HBV-DNA, hepatitis B virus deoxyribonucleic acid; HBeAg, hepatitis B e antigen; AFP, alpha-fetoprotein; WBC, white blood cell; PLT, platelet count; ALB, albumin; TBIL, total bilirubin; ALBI grade, albumin-bilirubin grade.

recurrence in patients with HBV-related HCC after hepatectomy (Yan et al., 2013; Zhu et al., 2018). In the study of Yan et al., (2013) they only analyzed efficacy of combined treatment on RFS. In the study of Yin Zhu et al, they analyzed efficacy of combined treatment on RFS and OS. But there were only 120 patients and more than half received TACE alone. In this study, we used a large patient cohort to investigate the long-term outcomes of this combined treatment strategy for HBV-related HCC with MVI after resection. We found that this combined treatment strategy may improve long-term outcomes in these patients.

MVI has been recognized as a risk factor for outcome following curative resection in HCC (Roayaie et al., 2009; Lim et al., 2011; Zhang et al., 2018). Because approximately 41-48% of resected HCC are accompanied by MVI (Chan et al., 2018; Erstad and Tanabe, 2019). Many researchers had focused on treating MVI to reduce recurrence and prolong survival (Rodriguez-Peralvarez et al., 2013; Erstad and Tanabe, 2019). In recent years, postoperative TACE demonstrated a beneficial treatment for HCC patients with MVI (Wang et al., 2018; Wei et al., 2018; Liu et al., 2019). In our study, postoperative TACE was the independent protected factors for OS (HR=0.75, 95%CI=0.64-0.87, p<0.01) and RFS (HR=0.88, 95%CI=0.77-1.01, p=0.07).

In HBV-related HCC, HBV viral loads and viral mutations are important risk factors for tumor recurrence after hepatic resection (Su et al., 2013; Sasaki et al., 2017), and previous studies suggest that nucleoside analogues treatment after curative resection for HBV-related HCC is associated with a reduced risk of recurrence and may prolong survival (Huang et al., 2015; Liu et al., 2016; Huang et al., 2018). Our result indicated that postoperative adjuvant AVT was the independent protected factors for OS (HR=0.65, 95%CI=0.56-0.76, p<0.01) and RFS (HR=0.75, 95%CI=0.66-0.86, p<0.01).

There are some limitations to our study. Firstly, postoperative AVT has been reached a consensus on guidelines at present. Because our study is a retrospective study, some patients didn't receive postoperative AVT. Secondly, the frequency, drugs, and dosages of postoperative TACE could vary across medical centers. Thirdly, this study was performed in China and most HCC patients had HBV infection, further validation is necessary for different geographic regions.

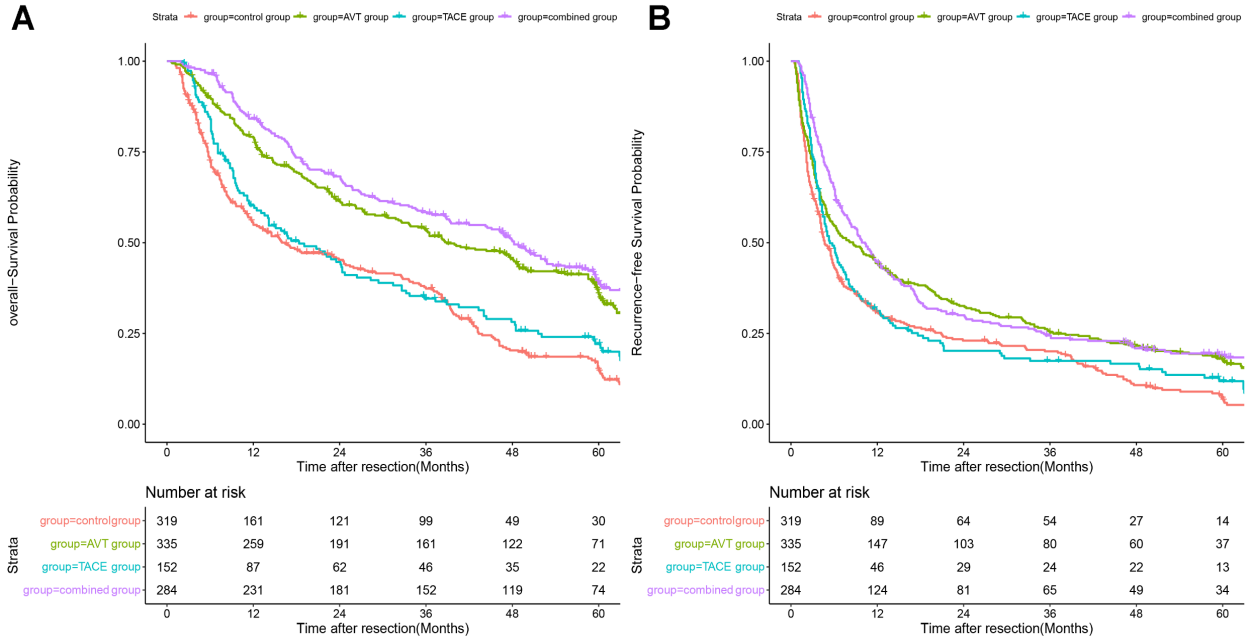

Figure 2. Kaplan-Meier Analysis of Prognosis among Four Groups. (A) overall survival; (B) recurrence-free survival. Abbreviations: AVT, antiviral therapy; TACE, transarterial chemoembolization.

Table 2. Univariate and Multivariate Analysis of Overall Survival for HBV-related HCC with MVI.

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95%CI	p	HR	95%CI	p
Age (years)						
(≥50 vs <50)	0.92	0.79-1.06	0.24			
Gender						
(male vs female)	1	0.79-1.26	0.99			
HBV-DNA (IU/mL)						
(≥2000 vs <2000)	1.14	0.99-1.32	0.06			
HBeAg						
(positive vs negative)	1.17	0.98-1.40	0.07			
AFP (ng/mL)						
(≥400 vs <400)	1.64	1.42-1.89	<0.01	1.26	1.08-1.46	<0.01
WBC (10^9/L)						
(≥4 vs <4)	1	0.83-1.20	0.99			
PLT (10^9/L)						
(≥100 vs <100)	0.99	0.81-1.20	0.9			
ALB (g/L)						
(≥35 vs <35)	0.56	0.39-0.81	<0.01			
TBIL (μmol/L)						
(≥17.1 vs <17.1)	1.12	0.95-1.31	0.18			
ALBI grade						
(Grade 2 vs Grade 1)	1.3	1.10-1.53	<0.01			
Surgical margin (cm)						
(≥1 vs <1)	1.62	1.32-1.99	<0.01	1.26	1.01-1.56	0.04
Blood transfusion						
(Yes vs No)	1.68	1.40-2.01	<0.01			
Blood loss (ml)						
(≥800 vs <800)	1.49	1.22-1.82	<0.01			
Tumor size (cm)						
(≥5 vs <5)	2.48	2.11-2.91	<0.01	1.87	1.55-2.25	<0.01
Tumor number						
(Multiple vs Solitary)	1.47	1.25-1.72	<0.01			
Differentiation						
(III-IV vs I-II)	1.83	1.26-2.66	<0.01			
Tumor capsular						
(No vs Yes)	1.88	1.62-2.18	<0.01	1.69	1.44-1.98	<0.01
Liver Cirrhosis						
(F1 vs F0)	1.05	0.89-1.25	0.57			
AVT						
(Yes vs No)	0.52	0.45-0.60	<0.01	0.65	0.56-0.76	<0.01
TACE						
(Yes vs No)	0.79	0.68-0.91	<0.01	0.75	0.64-0.87	<0.01

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MVI, microvascular invasion; AFP, alpha-fetoprotein; WBC, white blood cell; PLT, platelet count; ALB, albumin; TBIL, total bilirubin; ALBI grade, albumin-bilirubin grade; AVT, antiviral therapy; TACE, transarterial chemoembolization; HR, hazard ratio; CI, confidence interval.

In conclusion, postoperative adjuvant TACE and AVT were the independent protective factor associated with mortality and tumor recurrence in HBV-related HCC with MVI after resection. Considering the high rate of postoperative recurrence of HBV-related HCC with MVI, this combined treatment strategy may provide useful clinical significance in the prevention of tumor recurrence in these patients.

Abbreviations

HCC, hepatocellular carcinoma; AVT, antiviral therapy; TACE, transarterial chemoembolization;

Table 3. Univariate and Multivariate Analysis of Recurrence-Free Survival for HBV-related HCC with MVI

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	p	HR	95%CI	p
Age (years)						
(≥50 vs <50)	0.83	0.73-0.94	0.01			
Gender						
(male vs female)	1.16	0.94-1.43	0.17			
HBV-DNA (IU/mL)						
(≥2000 vs <2000)	1.24	1.09-1.41	<0.01			
HBeAg						
(positive vs negative)	1.04	0.89-1.21	0.65			
AFP (ng/mL)						
(≥400 vs <400)	1.61	1.41-1.83	<0.01	1.24	1.08-1.42	<0.01
WBC (10^9/L)						
(≥4 vs <4, 10^9/L)	1.01	0.85-1.19	0.95			
PLT (10^9/L)						
(≥100 vs <100)	0.95	0.79-1.13	0.57			
ALB (g/L)						
(≥35 vs <35)	0.69	0.49-0.97	0.03			
TBIL (μmol/L)						
(≥17.1 vs <17.1,)	1.06	0.91-1.22	0.47			
ALBI grade						
(Grade 2 vs Grade 1)	1.26	1.09-1.47	<0.01			
Surgical margin (cm)						
(≥1 vs <1)	1.5	1.26-1.80	<0.01			
Blood transfusion						
(Yes vs No)	1.51	1.28-1.79	<0.01			
Blood loss (ml)						
(≥800 vs <800)	1.43	1.19-1.72	<0.01			
Tumor size (cm)						
(≥5 vs <5)	2.19	1.90-2.52	<0.01	1.73	1.47-2.04	<0.01
Tumor number						
(Multiple vs Solitary)	1.63	1.41-1.88	<0.01	1.54	1.24-1.92	<0.01
Differentiation						
(III-IV vs I-II)	1.7	1.24-2.33	0.01			
Tumor capsular						
(No vs Yes)	1.63	1.43-1.87	<0.01	1.33	1.15-1.54	<0.01
Liver Cirrhosis						
(F1 vs F0)	1.12	0.96-1.31	0.147			
AVT						
(Yes vs No)	0.71	0.63-0.81	<0.01	0.75	0.66-0.86	<0.01
TACE						
(Yes vs No)	0.86	0.76-0.98	0.03			

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MVI, microvascular invasion; AFP, alpha-fetoprotein; WBC, white blood cell; PLT, platelet count; ALB, albumin; TBIL, total bilirubin; ALBI grade, albumin-bilirubin grade; AVT, antiviral therapy; TACE, transarterial chemoembolization; HR, hazard ratio; CI, confidence interval.

MVI, microvascular invasion; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus deoxyribonucleic acid; AFP, alpha-fetoprotein; WBC, white blood cell; HB, hemoglobin; PLT, platelet count; ALB, albumin; TBIL, total bilirubin; ALBI grade, albumin-bilirubin grade; BCLC, Barcelona Clinic Liver Cancer; OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval.

Author Contribution Statement

Conception and design: Zeng Jianxing, Tang Yupeng.

Administrative support: Jinhua Zeng. Provision of study materials or patients: Zeng Jianxing and Zeng Jinhua. Collection and assembly of data:Zhang Jinyu and Chen Guixiang. Data analysis and interpretation: Zhang Jinyu and Chen Guixiang. Manuscript writing: All authors. Final approval of manuscript: All authors.

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Conflict of interests

The authors declare no conflict of interest.

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