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ORIGINAL RESEARCH

Preoperative Antiviral Therapy and Long-Term Outcomes for Hepatitis B Virus-Related Hepatocellular Carcinoma After Curative Liver Resection: A Multicenter Analysis

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Background & Aims: To examine the association of the history of preoperative antiviral therapy (AVT) with the tumor recurrence and overall survival in HBV-related HCC patients undergoing curative-intent hepatectomy.

Methods: Patients who underwent curative-intent hepatectomy for HBV-related HCC between 2014 and 2019 at 4 Chinese hospitals were analyzed. Patients were categorized as having undergone preoperative antiviral therapy (AVT) > 1 year or without antiviral therapy (non-AVT). Patient clinical features, short-term outcomes, overall survival (OS), and time-to-recurrence (TTR) were also compared. Multivariate Cox regression analysis was performed to identify the impact of preoperative AVT on the OS and TTR.

Results: Among the 565 patients, 190 (33.6%) underwent continuous AVT > 1 year before surgery. Patients in the non-AVT group were more likely to have worse liver function and more advanced tumor pathological characteristics than those in the AVT group. Postoperative morbidity and mortality rates were comparable between the two groups. Multivariate analyses revealed that a preoperative HBV viral level ≥ 2000 IU/mL was independently associated with poorer TTR (hazard ratio, 1.328; 95% CI, 1.049–1.682) and preoperative AVT was a protective factor for OS (hazard ratio, 0.691; 95% CI, 0.484–0.986).

Conclusion: A high preoperative HBV DNA level was an independent risk factor for tumor recurrence. Preoperative AVT > 1 year was associated with better OS and a reduced incidence of tumor recurrence by inhibiting the preoperative level of HBV DNA.

Keywords: hepatectomy, hepatitis B virus, antiviral therapy, survival, recurrence

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and ranks as the fifth most prevalent tumor and second leading cause of cancer-related deaths worldwide.[1] Partial liver resection remains as the mainstay of curative modality used to treat HCC in appropriately selected patients.[2,3] Owing to the high recurrence and mortality rates of HCC, long-term prognosis outcomes remain unsatisfactory, despite patients undergoing radical treatment. Hepatitis B virus (HBV) infection is a significant risk factor for HCC, and China has the highest prevalence of HCC cases associated with HBV.[4,5]

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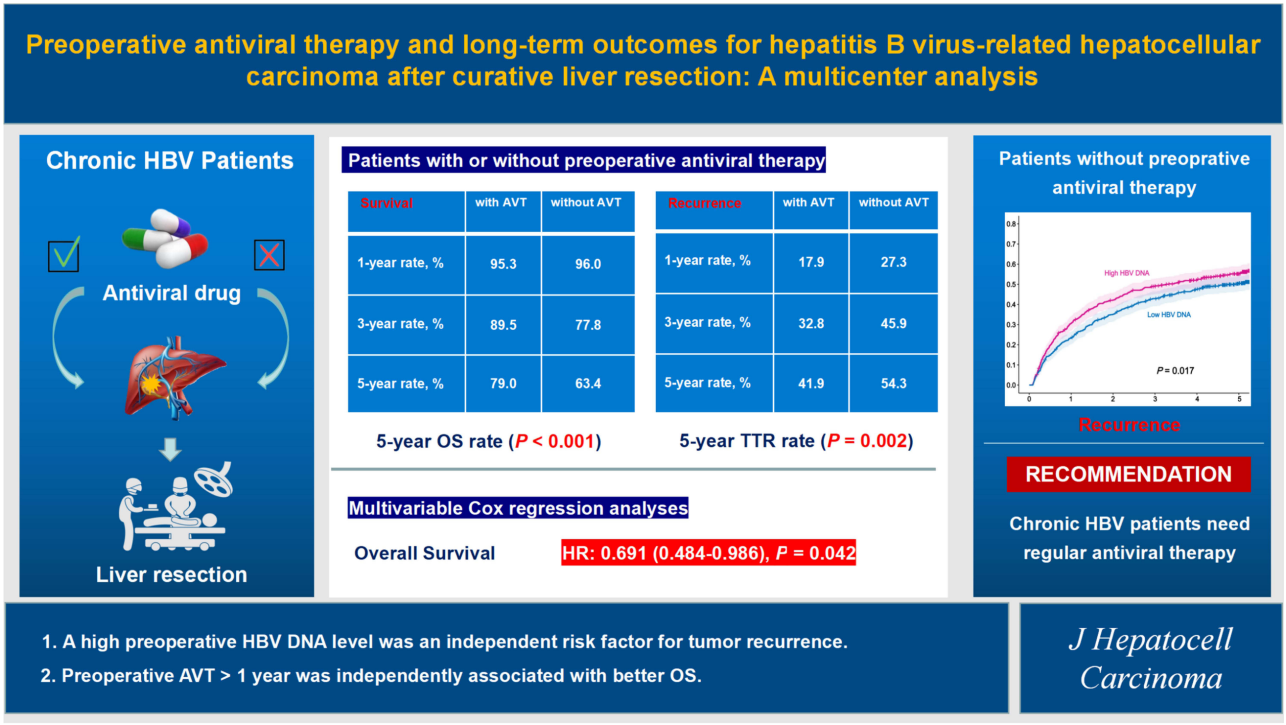
Graphical Abstract



However, a host of HCC patients commonly only become aware of their HBV infection when they seek medical attention because of symptoms caused by advanced tumors.[6,7] Previous studies have shown that long-term antiviral therapy (AVT) with nucleoside analogs (NAs) can reduce the incidence of HCC and prolong the survival of patients with chronic HBV infection.[8–11] A high preoperative HBV load is associated with postoperative recurrence.[12–14] Antiviral treatment after surgery for HBV-related HCC can reduce tumor recurrence and is widely used in clinical practice.[15–17] Preoperative short-term AVT has been reported to reduce early recurrence[18] and prolong OS.[19,20] Although many patients with chronic HBV infection receive long-term antiviral treatment, they still progress to HCC. Understanding the clinicopathological characteristics of patients receiving AVT compared with those who did not benefit from our clinical practice. However, studies on the correlation between preoperative long-term AVT and prognosis following surgery for HBV-related HCC are currently limited.

As such, the aim of current study was to investigate the clinicopathological features, perioperative outcomes and long-term oncologic prognosis of preoperative AVT versus non-AVT with HBV-related HCC.

Patients and Methods

Patients and Study Design

With the approval of the institutional review boards of all participating centers, a retrospective study was performed on a primary cohort of newly diagnosed patients who underwent curative hepatectomy between January 2015 and December 2019 at Zhejiang University Lishui Hospital, Zhejiang Provincial People's Hospital, Eastern Hepatobiliary Surgery Hospital, and ShaoXing Municipal Hospital in China. HCC was confirmed via postoperative pathological examination. Curative liver resection was defined as removal of HCC with a microscopically negative margin (R0 resection). All patients with HBV-related HCC, except for those with HBsAg seroclearance, were routinely treated with antiviral drugs after hepatectomy.

The inclusion criteria were as follows: 1) curative-intent resection, 2) no history of previous anti-cancer therapy, 3) no history of other malignancies, 4) HBV-related HCC, and 5) an Eastern Cooperative Oncology Group (ECOG) status score less than 2. The exclusion criteria were as follows: 1) gross vascular invasion, 2) recurrent HCC, 3) incomplete preoperative or postoperative follow-up medical records, and 4) palliative resection and presence of tumor rupture. Informed consent was obtained from all patients to be used for the research. This study was performed in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Studies in all participating hospitals.

Clinicopathological Characteristics and Operative Variables

Risk factors for survival and recurrence were evaluated as categories related to the patient, tumor, and treatment. Patient-related variables included age, sex, American Society of Anesthesiologists (ASA) score, serum Hepatitis B Surface Antigen (HBsAg) seroclearance, presence of cirrhosis or portal hypertension, albumin-bilirubin score (ALBI),[21] Child-Pugh grade, preoperative serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and preoperative HBV DNA level. Portal hypertension was defined as the presence of esophageal varices or splenomegaly with a decreased platelet count ($\leq 100\times10^9$/L). Tumor-related variables included preoperative serum alpha-fetoprotein (AFP) level, largest tumor diameter, tumor number (solitary or multiple), microvascular invasion (MVI) (negative or positive), satellite (negative or positive), tumor differentiation, tumor encapsulation, and tumor stage identified by the Barcelona Clinic Liver Cancer (BCLC) staging system.[22] Operative variables included intraoperative blood loss ($\leq$ 400 mL or > 400 mL), intraoperative blood transfusion (negative or positive), extent of liver resection (minor or major), type of hepatectomy (anatomical or non-anatomical), and resection margin status. Cirrhosis and tumor-related variables were diagnosed using imaging studies, including ultrasonography, contrast-enhanced computed tomography (CT), and magnetic resonance imaging (MRI) of the abdomen. Major hepatectomy was defined as the removal of three or more Couinaud's segments through partial hepatectomy, whereas minor hepatectomy involved the removal of fewer than three segments. Anatomical resections were determined according to the Brisbane 2000 nomenclature of liver anatomy.[23] Non-anatomical resections include limited or wedge resection.

Follow-Up and Primary Outcomes

Patients included in this study were closely monitored by both participating hospitals using a comprehensive surveillance strategy. Following discharge from the hospital, the patients underwent regular follow-up examinations at intervals of 2–3 months for the first 6 months, 3–4 months for the subsequent one and year, and every 3–6 months thereafter. These examinations included measurements of serum alpha-fetoprotein (AFP) and prothrombin induced by Vitamin K Absence-II (PIVKA II) levels as well as abdominal ultrasound, CT, or MRI. When HCC recurrence was suspected, contrast-enhanced CT or MRI, bone scan, or positron emission tomography was performed as clinically indicated.[24,25] Tumor recurrence was defined as the new appearance of an intra- or extra-hepatic nodule(s), with or without an increase in serum AFP or PIVKA II levels, which had typical imaging features consistent with the characteristics of HCC on enhanced CT or MRI examinations. Patients with tumor recurrence were actively treated with re-resection, TACE, percutaneous local ablation, radiotherapy, oral sorafenib, lenvatinib, or conservative treatment either alone or in combination. The primary endpoints of this study were survival and recurrence rates. At the time of initial recurrence, detailed information regarding the recurrence patterns and primary treatment received was documented.

Study Endpoints

The main goal of this study was to examine the long-term outcomes of patients. These outcomes included two primary endpoints, overall survival (OS) and time-to-recurrence (TTR). OS was defined as the period from the date of liver resection to either the date of death or the date of the last follow-up, which was crucial in determining the effectiveness of the treatment and assessing its impact on patients' life expectancy. TTR was defined as the time from surgery to tumor recurrence or the occurrence of new HCC, which aimed to evaluate the effectiveness of surgical intervention in

preventing tumor recurrence. For TTR, patients who died without tumor recurrence were censored at the last documented assessment.

Statistical Analysis

Clinical characteristics, operative variables, perioperative outcomes, and long-term outcomes were compared between the two groups. Statistical analyses were performed using SPSS software (version 25.0; SPSS, Chicago, IL, USA). Categorical variables are expressed as numbers or proportions, while continuous variables are expressed as mean ± standard deviation or median (range). Fisher's exact test and Wilcoxon rank-sum test were used for categorical and continuous variables, respectively. The OS and TTR rates were calculated using the Kaplan-Meier method and compared using the Log rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed using forward stepwise variable selection. Variables with a $P < 0.1$ on univariable analysis, were subjected to multivariable Cox regression analysis. *Statistical significance was set at* $P < 0.05$.

Results

Comparisons Clinicopathologic Characteristics

During the study period, 565 consecutive patients who underwent curative-intent liver resection for HBV-related HCC met the inclusion criteria (Figure 1). A total of 34 (6.0%) HBV-related HCC patients achieved HBsAg seroclearance before surgery. Clinicopathological characteristics of patients in the non-AVT and AVT groups were compared. Regarding clinicopathological variables, patients in the AVT group patients less often had lower preoperative ALT (11.1% vs 31.2%), AST (7.9% vs 24.8%), and HBV DNA levels (7.4% vs 52.5%). The proportion of patients with the largest tumor size of > 5 cm (25.3 vs 45.9%) and satellites (4.2% vs 12.8%) was higher among patients without AVT (all $P < 0.05$). Therefore, there was a statistically significant difference in the BCLC stage between the two groups ($P = 0.003$). As for operative variables, the operation time was longer, and the proportion of major hepatectomy and non-anatomical hepatectomy was higher in the non-AVT group (all $P < 0.05$).

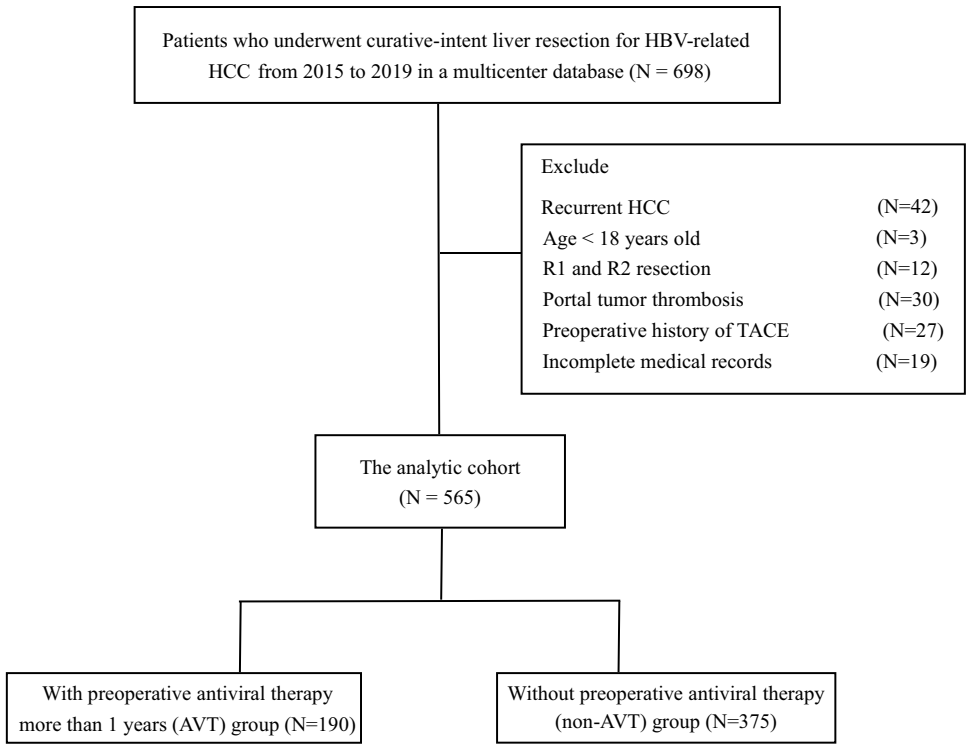


Figure 1 Selection of the study population.

Comparisons of Perioperative and Long-Term Outcomes

With respect to perioperative outcomes, there were no differences between AVT and non-AVT patients, including the incidence of postoperative 30-day morbidity (overall, minor, or major), mortality, 90-day mortality, and duration of postoperative hospital stay (all $P > 0.05$), as shown in Table 1. After excluding postoperative early deaths, a comparison of long-term outcomes between the two groups is shown in Table 2. The overall incidence of recurrence in patients receiving AVT was lower than those not receiving AVT ($P = 0.004$), but there were no differences in the patterns (intrahepatic, extrahepatic, or both) and BCLC stage of the initial recurrence. 22.6% patients in the AVT groups, 22.6%

Table 1 Baseline Characteristics of the Patients in the Two Cohorts

N (%)	Total (N = 565)	Without Preoperative Regular Antiviral Therapy (N = 375)	With Preoperative Regular Antiviral Therapy (N = 190)	P value
Clinicalpathologic Characteristics				
Age, years	55±12	55±13	55±11	0.869
Male	478 (84.6)	317 (84.5)	161 (84.7)	1.000
ASA score>2	94 (16.6)	66 (17.6)	28 (14.7)	0.406
Body mass index > 24 Kg/m^2	278 (49.2)	180 (48.0)	98 (51.6)	0.475
HBsAg seroclearance	34 (6.0)	24 (6.4)	10 (5.3)	0.709
HBeAg positive	122 (21.6)	68 (18.1)	54 (28.4)	0.005
Cirrhosis	384 (68.0)	252 (67.2)	132 (69.5)	0.651
Portal hypertension	108 (19.1)	67 (17.9)	41 (21.6)	0.344
ALBI grade 2/3	106 (18.8)	77 (20.5)	29 (15.3)	0.130
Child-Pugh grade B	25 (4.4)	20 (5.3)	5 (2.6)	0.139
Preoperative ALT level > 40 U/L	138 (24.4)	117 (31.2)	21 (11.1)	<0.001
Preoperative AST level > 40 U/L	108 (19.1)	93 (24.8)	15 (7.9)	<0.001
Preoperative AFP level > 400 μg/L	133 (23.5)	95 (25.3)	38 (20.0)	0.173
Preoperative HBV DNA level > 2000 IU/mL	211 (37.3)	197 (52.5)	14 (7.4)	<0.001
BCLC tumor stage				
BCLC 0/A	484 (85.6)	308 (82.1)	176 (92.6)	0.003
BCLC B	36 (6.4)	30 (8.0)	6 (3.2)	
BCLC C	45 (8.0)	37 (9.9)	8 (4.2)	
Largest tumor diameter > 5 cm	205 (36.3)	157 (41.9)	48 (25.3)	<0.001
Multiple Tumors	57 (10.1)	39 (10.4)	18 (9.5)	0.770
Microvascular invasion	202 (35.8)	139 (37.1)	63 (33.2)	0.411
Satellites	56 (9.9)	48 (12.8)	8 (4.2)	0.001
Poor tumor differentiation	516 (91.3)	345 (92.0)	171 (90.0)	0.432
Incomplete tumor encapsulation	391 (69.2)	264 (70.4)	127 (66.8)	0.442

(*Continued*)

Table 1 (Continued).

N (%)	Total (N = 565)	Without Preoperative Regular Antiviral Therapy (N = 375)	With Preoperative Regular Antiviral Therapy (N = 190)	P value
Operative Variables				
Operation time	115 (90–145)	120 (95–153)	105 (88–135)	0.001
Intraoperative blood loss > 400 mL	119 (21.1)	86 (22.9)	33 (17.4)	0.155
Intraoperative blood transfusion	26 (4.6)	22 (5.9)	4 (2.1)	0.054
Major liver resection	90 (15.9)	72 (19.2)	18 (9.5)	0.002
Non-anatomical liver resection	482 (85.3)	310 (82.7)	172 (90.5)	0.012
Resection margin < 1cm	387 (68.5)	267 (71.2)	120 (63.2)	0.065
Perioperative Outcomes				
Postoperative 30-day morbidity	178 (33.6)	125 (35.5)	53 (30.0)	0.189
Minor morbidity	142 (25.1)	98 (26.1)	44 (23.2)	0.441
Major morbidity	36 (6.4)	27 (7.2)	9 (4.7)	0.281
Postoperative 30-day mortality	1 (0.2)	1 (0.3)	0 (0.0)	1.000
Postoperative 90-day mortality	2 (0.4)	2 (0.5)	0 (0.0)	0.553
Postoperative hospital stays, days	7 (7–8)	7 (7–9)	7 (7–8)	0.606

Abbreviations: AFP, Alpha-fetoprotein; ASA, American Society of Anesthesiologists; ALBI, albumin-bilirubin; AST, aspartate transaminase; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen.

Table 2 Long-Term Outcomes After Excluding Postoperative Early Deaths (Postoperative 90-Day Mortality)

N (%)	Total (N = 563)	Without Preoperative Regular Antiviral Therapy (N = 373)	With Preoperative Regular Antiviral Therapy (N = 190)	P value
Recurrence during the follow-up	291 (51.7)	209 (56.0)	82 (43.2)	0.004
Intrahepatic recurrence	270 (92.8)	192 (91.9)	78 (95.1)	0.348
Extrahepatic recurrence	5 (1.7)	5 (2.4)	0 (0.0)	
Intra- and extrahepatic recurrence	16 (5.5)	12 (5.7)	4 (4.9)	
BCLC stage of initial recurrence	291 (51.7)	209 (56.0)	82 (43.2)	0.004
BCLC A stage	182 (62.5)	127 (60.8)	55 (67.1)	0.378
BCLC B stage	72 (24.7)	52 (24.9)	20 (24.4)	
BCLC C stage	37 (24.8)	30 (14.3)	7 (8.5)	
Mortality during the follow-up	190 (33.7)	147 (39.4)	43 (22.6)	<0.001
Cancer-specific mortality	155 (81.6)	122 (83.0)	33 (76.7)	0.371
Non-cancer-specific mortality	35 (18.4)	25 (17.0)	10 (23.3)	

(*Continued*)

Table 2 (Continued).

N (%)	Total (N = 563)	Without Preoperative Regular Antiviral Therapy (N = 373)	With Preoperative Regular Antiviral Therapy (N = 190)	P value
Median overall survival (OS), 95% CI	61 (47–69)	61 (42–68)	61 (53–70)	0.005
1-year OS rate, %	95.7	96.0	95.3	<0.001
3-year OS rate, %	81.9	77.8	89.5	
5-year OS rate, %	68.6	63.4	79.0	
Median time-to-recurrence (TTR), 95% CI	48 (13–64)	61 (12–64)	61 (19–66)	0.007
1-year TTR rate, %	24.2	27.3	17.9	0.002
3-year TTR rate, %	41.5	45.9	32.8	
5-year TTR rate, %	50.1	54.3	41.9	

and 39.4% of the patients in the non-AVT group died during follow-up, but the proportions of cancer-specific and non-cancer-specific mortality between the two groups were similar ($P = 0.371$). The OS and TTR among patients receiving AVT versus those not receiving AVT are shown in Figure 2A and B, respectively. The 1-, 3-, and 5-year OS rates in the AVT and non-AVT group patients were 95.3%, 89.5%, and 79.0% vs 96.0%, 77.8%, and 63.4%, respectively, and the difference in OS between the two groups was significant ($P < 0.01$). Meanwhile, the1-, 3-, and 5-year TTR rates for patients in the AVT and non-AVT groups were 17.9%, 32.8%, and 41.9% versus 27.3%, 45.9%, and 54.3%, respectively, and the difference in TTR between the groups was significant ($P = 0.002$).

Prognostic Analyses of OS and TTR in the Whole Cohort

Tables 3 and 4 describe the risk factors associated with OS and TTR after hepatectomy for HBV-related HCC, which were examined using univariate and multivariate Cox regression analyses, respectively. After adjusting for other confounding factors, preoperative AVT was independently associated with better OS (hazard ratio, 0.691; 95% confidence interval: 0.484–0.986, P = 0.042) but not poorer TTR (P = 0.371).

Prognostic analyses of OS and TTR in the non-AVT cohort.

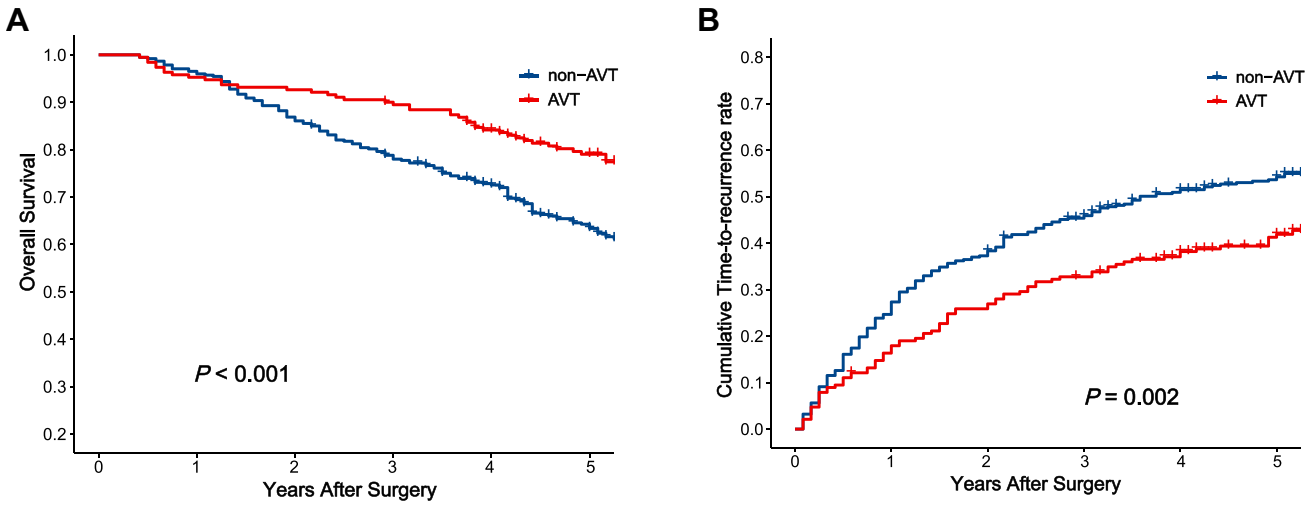


Figure 2 Curves comparisons of survival (**A**) and recurrence (**B**) between two groups in the whole cohort (calculated by Log rank test).

Table 3 Univariable and Multivariable Cox Regression Analyses of Preoperative Predictive Factors for Survival

Variables	HR Comparison	UV HR (95% CI)	UV *P*	MV HR (95% CI)	MV *P*
Age	> 60 vs ≤ 60 years	1.467 (1.094–1.967)	0.010	NA	0.935
Sex	Male vs Female	1.182 (0.781–1.788)	0.428		
ASA score	> 2 vs ≤ 2	1.797 (1.288–2.505)	0.001	1.706 (1.216–2.394)	0.002
Body mass index	> 24 vs ≤ 24 Kg/m^2	0.675 (0.506–0.901)	0.008	0.743 (0.555–0.996)	0.047
Cirrhosis	Presence vs Absence	1.697 (1.221–2.360)	0.002	1.700 (1.204–2.402)	0.003
Portal hypertension	Presence vs Absence	1.018 (0.708–1.463)	0.925		
ALBI score	2/3 vs 1 grade	1.800 (1.305–2.483)	< 0.001	NA	0.270
Preoperative ALT level	> 40 vs ≤ 40 U/L	1.783 (1.320–2.409)	< 0.001	1.394 (1.016–1.913)	0.040
Preoperative AST level	> 40 vs ≤ 40 U/L	1.754 (1.269–2.423)	0.001	NA	0.969
Preoperative AFP level	> 400 vs ≤ 400 μg/L	1.629 (1.194–2.222)	0.002	NA	0.191
Preoperative HBV-DNA level	≥ 2000 vs < 2000 IU/mL	1.336 (1.003–1.779)	0.048	NA	0.693
Largest tumor diameter	> 5 vs ≤ 5 cm	2.711 (2.037–3.610)	< 0.001	2.328 (1.729–3.135)	< 0.001
Tumor number	Multiple vs Solitary	1.883 (1.260–2.813)	0.001	2.051 (1.363–3.085)	0.001
Microvascular invasion	Yes vs no	1.917 (1.441–2.549)	0.002	1.688 (1.261–2.260)	< 0.001
Satellites	Yes vs no	2.392 (1.635–3.499)	< 0.001	NA	0.617
Poor tumor differentiation	Yes vs no	2.926 (1.375–6.225)	0.005	2.235 (1.090–5.004)	0.029
Incomplete tumor encapsulation	Yes vs no	1.429 (1.034–1.975)	0.031	1.545 (1.112–2.145)	0.009
Intraoperative blood loss	> 400 vs ≤ 400 mL	1.730 (1.262–2.372)	0.001	NA	0.198
Extent of liver resection	Major vs ≤ Minor	2.162 (1.553–3.008)	< 0.001	NA	0.487
Non-anatomical liver resection	Yes vs no	0.847 (0.576–1.244)	0.397		
Resection margin	< 1 vs ≥ 1 cm	2.193 (1.519–3.167)	< 0.001	1.712 (1.179–2.484)	0.005
Preoperative antiviral therapy	Yes vs no	0.513 (0.365–0.721)	< 0.001	0.691 (0.484–0.986)	0.042

Abbreviations: AFP, Alpha-fetoprotein; ASA, American Society of Anesthesiologists; ALBI, albumin-bilirubin; AST, aspartate transaminase; ALT, alanine aminotransferase; CI, Confidence interval; HR, Hazard ratio; MV, multivariate; UV, univariate; NA, not available.

Table 4 Univariable and Multivariable Cox Regression Analyses of Preoperative Predictive Factors for Recurrence

Variables	HR Comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P
Age	> 60 vs ≤ 60 years	1.146 (0.895–1.465)	0.273		
Sex	Male vs Female	1.314 (0.934–1.848)	0.117		
ASA score	> 2 vs ≤ 2	1.204 (0.895–1.618)	0.220		
Body mass index	> 24 vs ≤ 24 Kg/m^2	0.831 (0.660–1.046)	0.115		
Cirrhosis	Presence vs Absence	1.787 (1.363–2.345)	< 0.001	1.611 (1.219–2.130)	0.001
Portal hypertension	Presence vs Absence	1.162 (0.874–1.545)	0.300		
ALBI grade	2/3 vs 1 grade	1.529 (1.165–2.009)	0.002	NA	0.371

(*Continued*)

Table 4 (Continued).

Variables	HR Comparison	UV HR (95% CI)	UV P	MV HR (95% CI)	MV P
Preoperative ALT level	> 40 vs ≤ 40 U/L	1.547 (1.204–1.988)	0.001	NA	0.192
Preoperative AST level	> 40 vs ≤ 40 U/L	1.509 (1.146–1.986)	0.003	NA	0.501
Preoperative AFP level	> 400 vs ≤ 400 μg/L	1.282 (0.984–1.672)	0.066	NA	0.849
Preoperative HBV-DNA level	≥ 2000 vs < 2000 IU/mL	1.466 (1.163–1.848)	0.001	1.361 (1.076–1.721)	0.010
Largest tumor diameter	> 5 vs ≤ 5 cm	2.052 (1.628–2.588)	< 0.001	1.782 (1.401–2.265)	< 0.001
Tumor number	Multiple vs Solitary	2.113 (1.522–2.932)	< 0.001	2.135 (1.531–2.977)	< 0.001
Microvascular invasion	Yes vs no	1.409 (1.114–1.782)	0.004	1.332 (1.050–1.690)	0.018
Satellites	Yes vs no	2.828 (2.058–3.885)	< 0.001	1.830 (1.310–2.556)	< 0.001
Poor tumor differentiation	Yes vs no	1.862 (1.155–3.155)	0.011	NA	0.052
Incomplete tumor encapsulation	Yes vs no	1.209 (0.939–1.557)	0.142		
Intraoperative blood loss	> 400 vs ≤ 400 mL	1.327 (1.010–1.743)	0.043	NA	0.765
Extent of liver resection	Major vs ≤ Minor	1.527 (1.138–2.049)	0.005	NA	0.847
Non-anatomical liver resection	Yes vs no	1.014 (0.708–1.362)	0.915		
Resection margin	< 1 vs ≥ 1 cm	1.677 (1.280–2.198)	< 0.001	1.355 (1.029–1.783)	0.030
Preoperative antiviral therapy	Yes vs no	0.674 (0.522–0.870)	0.002	NA	0.371

Abbreviations: AFP, Alpha-fetoprotein; ASA, American Society of Anesthesiologists; ALBI, albumin-bilirubin; AST, aspartate transaminase; ALT, alanine aminotransferase; CI, Confidence interval; HR, Hazard ratio; MV, multivariate; UV, univariate; NA, not available.

In the sub-analysis of the non-AVT cohort, the OS and TTR of patients with low HBV DNA levels versus those with high HBV DNA levels are shown in Figure 3A and B. Similarly, independent risk factors were identified in patients who did not undergo AVT using a multivariate Cox regression analysis as shown in Table 5. We found that high HBV DNA levels remained independent of an increased TTR (hazard ratio, 1.362; 95% confidence interval: 1.026–1.810, P = 0.032).

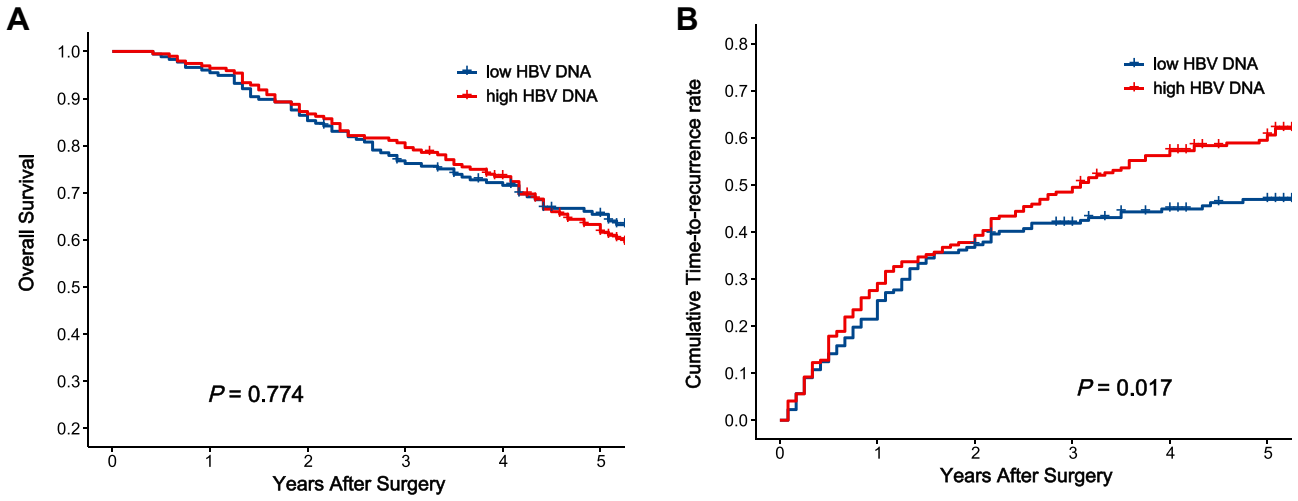


Figure 3 Curves comparisons of survival (**A**) and recurrence (**B**) between two groups in the non-AVT cohort (calculated by Log rank test).

Table 5 Independent Risk Factors Associated with Overall Survival (OS) and Time-to-Recurrence (TTR) in Patients Not Receiving AVT After Liver Resection for HBV-Related Hepatocellular Carcinoma

Independent Risk Factors	MV HR (95% CI)	MV P
Overall Survival		
ASA score>2	1.582 (1.076–2.327)	0.020
Microvascular invasion	1.829 (1.303–2.568)	< 0.001
Multiple Tumors	2.179 (1.371–3.463)	0.001
Preoperative AFP level > 400 μg/L	1.444 (1.006–2.073)	0.046
Largest tumor diameter > 5 cm	2.233 (1.598–3.121)	< 0.001
Incomplete tumor encapsulation	1.852 (1.254–2.736)	0.002
Cirrhosis	2.102 (1.408–3.139)	< 0.001
Time-to-recurrence		
Microvascular invasion	1.335 (1.005–1.773)	0.046
Multiple Tumors	2.231 (1.503–3.310)	< 0.001
Satellites	1.793 (1.237–2.598)	0.002
Largest tumor diameter > 5 cm	1.798 (1.353–2.390)	< 0.001
Incomplete tumor encapsulation	1.370 (1.004–1.870)	0.047
Cirrhosis	1.938 (1.380–2.722)	< 0.001
Preoperative HBV DNA level > 2000 IU/mL	1.362 (1.026–1.810)	0.032

Discussion

The present multicenter study from China analyzed the clinicopathological characteristics and short- and long-term outcomes of curative hepatectomy for HBV-related HCC. In this study, only 190 (33.6%) HCC patients received regular antiviral therapy before surgery, indicating the neglect of HBV infection and ignorance of disease progression by the patients. Patients who did not receive any AVT preoperatively were more likely to have high preoperative HBV DNA levels and advanced tumor pathological features (proportion of tumor size > 5 cm, satellites, and BCLC stage B/C) than those who received AVT for more than 1 year. Short-term outcomes, including postoperative mortality and morbidity, were comparable between the AVT and non-AVT groups. Patients who underwent continuous preoperative AVT had better OS than those who did not. In addition, a viral level of > 2000 IU/mL was significantly associated with increased HCC recurrence after partial liver resection. Eliminating social discrimination against HBV, strengthening communication between doctors and patients, and enhancing the awareness of HBV patients about the disease may increase the antiviral treatment rate.

Numerous previous studies have shown that HBeAg-positive status in patients with chronic HBV infection is a significant risk factor for HCC.[26–28] Interestingly, the proportion of HBeAg-positive in AVT group was significantly higher in the AVT group than that in the non-AVT group. If patients with chronic HBV who have received AVT remain HBeAg-positive, more attention should be paid to HBV control and regular screening for HCC development. The preoperative AVT group exhibited a relatively lower tumor burden, potentially owing to the heightened awareness of liver cancer prevention among these patients. In this study, HCC patients who received preoperative AVT demonstrated superior liver function reserve, which may contribute to better OS.[29]

In this cohort, all patients with HBV-related HCC except those with HBsAg seroclearance were routinely treated with antiviral drugs after hepatectomy.[30] Tenofovir disoproxil might be associated with better long-term OS and RFS rates compared with entecavir for HBV-related HCC patients undergoing curative liver resection.[31] Portal vein tumor thrombosis (PVTT) is an independent factor of 90-day mortality and long-term outcomes.[32] We excluded the HCC patients with PVTT due to the effect of preoperative antiviral therapy was easily overshadowed by the extremely high-risk factor. To explore the association between preoperative AVT and HBV DNA and long-term prognosis in patients with HCC who underwent liver resection, it may be more intuitive to further divide preoperative AVT and non-AVT patients into four groups based on the level of HBV DNA to demonstrate their potential relationship. However, because only 14 (7.4%) patients in the preoperative AVT group had viral levels of > 2000 IU/mL, further analysis was not possible. Therefore, subgroup analysis was performed in the non-AVT cohort, and the results showed that a high preoperative viral level was still an independent risk factor for recurrence but not for overall survival. Several previous studies have suggested that preoperative antiviral therapy may reduce the incidence of MVI for HBV-related HCC.[18,33] Concerning 2362 HBV-related HCC patients who underwent liver resection, Li et al demonstrated that antiviral treatment administered more than 90 days before surgery was associated with early tumor recurrence by reducing the incidence of MVI.[18] Huang et al further reported that preoperative antiviral therapy can prolong survival and decrease the recurrence rate of patients with recurrent HCC.[34] However, it was not an independent risk factor for recurrence, although the survival curves indicated that the preoperative AVT group performed significantly better than the non-AVT group did. In our opinion, this result may be due to the fact that preoperative antiviral drugs indirectly affect the recurrence by controlling the level of viral DNA. The effect of antiviral drugs on improving OS in our study is consistent with the results of previous studies.[20,34,35]

Our study has some limitations. First, the study was retrospective in nature, which could have led to inherent bias. In addition, chronic HBV infection is the leading etiology of HCC in China and many Asian countries, and is distinct from the pattern of disease seen in the United States and other Western countries. Furthermore, owing to the retrospective nature of the study, the specific antiviral duration of each patient could not be determined; therefore, the optimal preoperative antiviral duration could not be further analyzed.

Ethics Approval and Consent to Participate

The study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards of all the participating hospitals.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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