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ORIGINAL RESEARCH

Postoperative hepatitis B virus reactivation in hepatitis B virus-related hepatocellular carcinoma patients with hepatitis B virus DNA levels <500 copies/mL

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Background: Patients with hepatocellular carcinoma have the risk of postoperative hepatitis B virus (HBV) reactivation (PHR). Antiviral therapy was given to patients with detectable HBV DNA levels but not to patients with undetectable HBV DNA levels.

Methods: In this retrospective study, 258 patients were enrolled (HBV DNA levels <500 copies/mL group, n=159, and HBV DNA levels >500 copies/mL group, n=99).

Results: A total of 50 patients (19.4%) had PHR. The following significant factors related to PHR were found: without antiviral therapy (hazard ratio [HR] =0.17, 95% confidence interval [CI] 0.031–0.911), hepatitis B e antigen positivity (HR =5.20, 95% CI 1.931–14.007), hepatitis B core antigen S1 positivity (HR =2.54, 95% CI 1.116–5.762), preoperative HBV DNA levels ≥500 copies/mL (HR =1.28, 95% CI 1.085–2.884), hepatic inflow occlusion (HR =3.60, 95% CI 1.402–9.277), moderate liver cirrhosis or more (HR =2.26, 95% CI 1.001–5.121), and blood transfusion (HR =2.89, 95% CI 0.836–10.041). Recurrence-free survival time was significantly shorter in patients with PHR (23.06±2.46 months) than in patients without PHR (29.30±1.27 months).

Conclusion: Antiviral therapy could efficiently decrease the incidence of PHR. Patients with HBV DNA levels <500 copies/mL still have the risk of PHR. PHR remained as a prognostic risk factor for hepatocellular carcinoma recurrence and recurrence-free survival.

Keywords: hepatocellular carcinoma, hepatitis B virus, postoperative reactivation, hepatectomy, HBV DNA levels

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer in the world and is the third leading cause of cancer-related death.[1] Hepatitis B virus (HBV) infection is the major risk factor for HCC patients, especially in Asia-Pacific region.[2–4]

Because of the high incidence of postoperative HCC recurrence, overall survival (OS) of HCC patients remains relatively low, despite surgery being a curative therapy.[5,6] However, postoperative HBV reactivation (PHR) is one significant factor[7,8] that contributes to HCC recurrence. Several trials[9–12] and our previous study[13] found that PHR occurs after hepatectomy in HBV-related HCC (HBV-HCC) patients. Hepatitis B e antigen (HBeAg), preoperative HBV DNA level, liver cirrhosis degree, blood transfusion, operating time, and preoperative antiviral therapy are independent risk factors for PHR.[14] PHR occurs not only in HCC patients with high HBV DNA levels but also in HCC patients with low HBV DNA levels.[14–16] According to the guidelines from the Asian Pacific Association for the Study of the Liver,[17] antiviral

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therapy was available for patients with detectable HBV DNA levels. However, there are no obvious suggestions about using antiviral therapies in patients with undetectable HBV DNA levels.

Here, we aimed to evaluate the incidence of PHR in HBV-HCC patients with undetectable HBV DNA levels, thus finding out the difference of the short-term and long-term outcomes between patients with PHR and patients without PHR, with undetectable HBV DNA levels.

Patients and methods

Ethics statement

This study was approved by the Institutional Review Board of Guangxi Medical University and conducted in accordance with the Declaration of Helsinki and internationally accepted ethical guidelines. The patients enrolled in this study signed written consent during their admission for surgery for their information to be stored in hospital databases and used for research. During data collection, patient records were anonymized, as we previously mentioned in our former study.[13]

Patients

A total of 258 consecutive patients admitted to our hospital from 2011 to 2012 were retrospectively enrolled in our study. The inclusion criteria were as follows: 1) 18–75 years old; 2) HBV-infected HCC patients and first diagnosed in our hospital;[17] 3) Child-Pugh stages A to B; 4) resectable HCC patients;[18] and 5) HCC confirmed by postoperative pathology.

Patients were divided into two groups based on their HBV DNA levels (Group A: patients with HBV DNA levels <500 copies/mL and Group B: patients with detectable HBV DNA levels). HCC was diagnosed based on the criteria of the European Association for the Study of the Liver.[19]

Preoperative management

A baseline assessment of HBV DNA; the presence of hepatitis B surface antigen, HBeAg, and against hepatitis B core antigen S1; serum levels of alanine aminotransferase (ALT), aspartate aminotransferase, total bilirubin (TBil), and albumin (ALB); prothrombin time (PT); levels of α-fetoprotein (AFP); and proportions of several T-lymphocyte subpopulations ($CD3^+CD4^+$ and $CD3^+CD8^+$) were tested within 1 week before hepatectomy.

Serum levels of HBV DNA were quantified using the PCR-based Care HBV V2 Assay Kit (Qiagen NV, Venlo, the Netherlands) in which the lower limit of detection was 500 copies/mL (1 IU/mL =1 copy/mL).

Entecavir (0.5 mg once a day; Tai-Tianqing Pharmaceutical Co., Jiangsu, People's Republic of China) antiviral therapy was given to patients who fit the criteria of given antiviral therapy at least 3 days before hepatectomy.[20]

Surgical management

During hepatectomy, data on the surgical procedure, including tumor number, tumor diameter (the maximal tumor diameter), tumor rupture, complete capsule, surgical margin, tumor thrombus, hepatic inflow occlusion, operating time, blood loss, blood transfusion, and liver cirrhosis degree, were recorded.

Postoperative management

At the 1-month reexamination, the same blood tests and radiological examination as at baseline were repeated. Patients were monitored for PHR within postoperative 1 month. A tenfold increase in HBV DNA levels compared with preoperative levels as well as detectable level of HBV DNA postoperatively with undetectable level at baseline was defined as PHR.[14] Patients with PHR were given antiviral therapy once upon the detection of reactivation.

Outcomes and follow-up

The primary outcomes in our study were recurrence-free survival (RFS). We compared the difference of RFS between patients with HBV DNA levels >500 copies/mL and <500 copies/mL. Subgroup analysis of RFS was conducted based on the status of PHR. As secondary outcomes, we compared postoperative complications between two subgroups. These complications were evaluated using the Clavien-Dindo scoring system.[21]

Statistical analysis

All data analyses were performed using SPSS 21.0 (IBM Corporation, Armonk, NY, USA) and with $P<0.05$ defined as the threshold of statistical significance. Normally distributed data were expressed as mean ± SD, while asymmetrically distributed data were expressed as median (range). Differences in outcomes between two groups were assessed using independent samples *t*-tests for measurement data or χ^2 test for frequency of various attributes between groups. Factors significantly associated with PHR and HCC recurrence were identified first by univariate logistic regression, and then the significant univariate factors were examined by multivariate analysis using a stepwise logistic model. RFS curves were analyzed using the Kaplan–Meier method in which differences between curves were assessed using the log-rank test.

Comprehensive MEDLINE review

The following medical subject headings were comprehensively searched in the MEDLINE database: "hepatocellular carcinoma" or "primary liver carcinoma" or "primary liver cancer" or "liver cancer" or "liver tumor" and "hepatectomy" or "liver surgery" or "liver resection" or "hepatic resection" and "hepatitis B virus" and "reactivation". Based on the following criteria, relevant references and review articles were manually searched: 1) evaluated PHR in HBV-HCC patients, 2) were published in English, and 3) outcomes were about survival outcomes, PHR rate, and HCC recurrence. We selected only the study with the largest number of participants when several studies were based on the same population.

Results

Characteristics of the study population

From January 2011 to 2012, 1,004 potentially eligible HCC patients were admitted to our hospital for hepatic resection. A total of 258 HCC patients satisfying the inclusion and exclusion criteria were enrolled. Of the 258 HCC patients, 159 patients with HBV DNA levels <500 copies/mL were defined as Group A and the remaining 99 patients with detectable HBV DNA levels were defined as Group B. Baseline characteristics were similar between the two groups (Table 1). Of the 258 HCC patients enrolled, 33 (12.8%) patients with detectable HBV DNA levels were given antiviral therapy. After hepatectomy, 50 (19.4%) patients (24 patients with HBV DNA levels <500 copies/mL and 15.1% and 26 patients with detectable HBV DNA levels, 26.3%) had PHR. Of the 33 patients with antiviral therapy, one (3.0%) patient had PHR.

PHR

A total of 50 (19.4%) patients had PHR of whom one (1/33, 3.0%) patient was given antiviral therapy and the remaining 49 (49/225, 21.8%) patients were without antiviral therapy.

Table 1 Characteristics of Chinese patients with HBV-related hepatocellular carcinoma who underwent hepatic resection

Characteristics	Patients with HBV DNA <500 copies/mL (n=159)	Patients with detectable HBV DNA level (n=99)	*P*-value
Mean age ± SD (years)	48.33±11.38	49.69±10.22	0.335
Males, n (%)	141 (88.7)	83 (83.8)	0.264
Prophylactic antiviral therapy, n (%)	0 (0.0)	33 (33.3)	<0.001
Postoperative HBV reactivation, n (%)	24 (15.1)	26 (28.9)	0.027
Positive for HBeAg, n (%)	25 (15.7)	15 (16.7)	0.875
Positive for HBV-cAg S1, n (%)	83 (52.2)	56 (56.6)	0.494
PT (seconds)	12.81±1.22	13.34±3.67	0.168
TBil (μmol/L)	10.30 (7.70–14.00)	12.00 (8.70–16.10)	0.982
ALB (g/L)	41.90±4.48	40.95±4.89	0.110
ALT (IU/L)	32.00 (22.00–45.00)	39.00 (28.00–59.00)	0.320
AFP (ng/mL)	459.00 (7.50–12,100.00)	130.00 (11.00–12,100.00)	0.948
$CD3^+CD4^+$ (%)	33.56±8.16	35.67±10.41	0.497
$CD3^+CD8^+$ (%)	23.12±8.78	20.37±5.67	0.076
Tumor number	1.39±0.67	1.40±0.70	0.872
Tumor diameter (cm)	7.06±3.45	7.14±3.77	0.781
Tumor rupture, n (%)	8 (5.0)	5 (5.1)	0.995
Complete capsule, n (%)	102 (64.2)	63 (63.7)	0.933
Surgical margin (cm)	2.38±1.12	2.12±1.05	0.613
Tumor thrombus, n (%)	37 (23.3)	24 (24.2)	0.337
Hepatic flow occlusion, n (%)	113 (71.1)	72 (72.7)	0.774
Operating time (minutes)	186.89±62.45	198.22±64.26	0.845
Blood loss (mL)	300.00 (200.00–500.00)	350.00 (200.00–600.00)	0.675
Blood transfusion, n (%)	32 (20.1)	19 (19.2)	0.855
BCLC stage (A/B/C), n (%)	82 (51.6)/40 (25.2)/37 (23.3)	51 (51.5)/24 (24.2)/24 (24.2)	0.978
Degree of liver cirrhosis (0/1/2/3), n (%)	25 (15.7)/69 (43.4)/48 (30.2)/17 (10.7)	12 (12.1)/45 (45.5)/31 (31.3)/11 (11.1)	0.886
Cost (RMB)	55,349.64±11,649.67	56,649.16±16,377.7	0.184
Hospital stay (days)	18.27±7.24	19.16±10.37	0.934
Clavien-Dindo stage score	1.89±0.72	1.97±0.87	0.436

Note: Values are shown as mean ± SD, n (%), or average (range), unless otherwise indicated.

Abbreviations: AFP, α-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HBV-cAg S1, against hepatitis B core antigen S1; PT, prothrombin time; TBil, total bilirubin.

Table 2 Univariate and multivariate analyses of prognostic factors for HBV reactivation in Chinese patients with HBV-related HCC

Factor	Univariate analysis				Multivariate analysis		
	Patients, n (%)	HR	95% confidence interval	*P*-value	HR	95% confidence interval	*P*-value
Antiviral therapy							
Yes	33 (12.8)	0.24	0.055–1.030	<0.001	0.17	0.031–0.911	<0.001
No	225 (87.2)						
Positive for HBeAg							
Yes	40 (15.5)	6.27	3.021–13.001	<0.001	5.20	1.931–14.007	0.001
No	218 (84.5)						
HBV-cAg S1							
Yes	139 (53.9)	2.09	1.085–4.007	0.028	2.54	1.116–5.762	0.026
No	119 (46.1)						
Preoperative HBV DNA							
>500	99 (38.4)	1.81	0.971–3.376	0.022	1.28	1.085–2.884	0.030
<500	159 (61.6)						
Hepatic inflow occlusion							
Yes	185 (71.7)	3.93	1.712–9.005	0.031	3.60	1.402–9.277	0.008
No	73 (28.3)						
Degree of liver cirrhosis							
Light (0–1)	151 (58.5)	3.52	1.834–6.736	<0.001	2.26	1.001–5.121	0.049
Moderate or more (≥2)	107 (41.5)						
Operating time (minutes)							
>180	80 (31.0)	4.25	2.232–8.097	0.041	3.26	1.418–7.508	0.055
≤180	178 (69.0)						
Blood transfusion, n (%)							
Yes	51 (19.8)	4.85	2.451–9.596	<0.001	2.89	0.836–10.041	0.043
No	207 (80.2)						

Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HBV-cAg S1, against hepatitis B core antigen S1; HCC, hepatocellular carcinoma; HR, hazard ratio.

In patients with HBV DNA levels <500 copies/mL, 24 (15.1%) patients had PHR.

We conducted univariate and multivariate analyses and found the following significant factors related with PHR: without antiviral therapy (hazard ratio [HR] =0.17, 95% CI 0.031–0.911, $P<0.001$), HBeAg positivity (HR =5.20, 95% CI 1.931–14.007, $P=0.001$), against hepatitis B core antigen S1 positivity (HR =2.54, 95% CI 1.116–5.762, $P=0.026$), preoperative HBV DNA level of ≥500 copies/mL (HR =1.28, 95% CI 1.085–2.884, $P=0.030$), hepatic inflow occlusion (HR =3.60, 95% CI 1.402–9.277, $P=0.008$), moderate liver cirrhosis or more (HR =2.26, 95% CI 1.001–5.121, $P=0.049$), and blood transfusion (HR =2.89, 95% CI 0.836–10.041, $P=0.043$) (Table 2). Thus, HBV DNA levels >500 copies/mL and without preoperative antiviral therapy remained independent risk factors for PHR.

RFS

RFS (23.06±2.46 months) was significantly lower in patients with PHR than in patients without PHR (29.30±1.27 months, $P=0.014$) (Figure 1). One-year, 2-year, and 3-year RFS rates for patients with PHR were 75.8%, 38.1%, and 28.9%, respectively, and those for patients without PHR were 84.5%, 56.5%, and 40.7%, respectively.

We conducted univariate and multivariate analyses and found the following significant risk factors for RFS: PHR (HR =1.48, 95% CI 1.228–2.023, $P=0.047$), HBeAg positivity (HR =4.84, 95% CI 2.617–8.941, $P<0.001$),

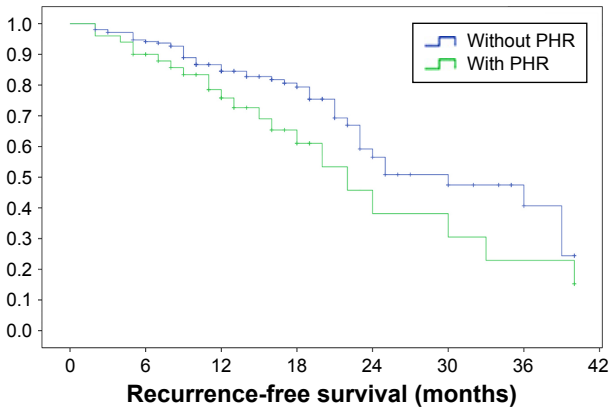

Figure 1 Recurrence-free survival between patients with HBV DNA levels <500 copies/mL and patients with detectable HBV DNA levels.
Abbreviations: HBV, hepatitis B virus; PHR, postoperative HBV reactivation.

surgical margin <1 cm (HR =0.53, 95% CI 0.290–0.964, *P*=0.038), moderate or serve liver cirrhosis (HR =1.88, 95% CI 1.040–3.377, *P*=0.036), and blood transfusion (HR =3.25, 95% CI 1.691–6.213, *P*<0.001) (Table 3).

Subgroup analysis of RFS depending on antiviral therapy was also conducted. We found that patients with and without antiviral therapy had similar RFS (28.13 months and 27.82 months, respectively, *P*=0.996).

Postoperative complications and recurrence

Postoperative Clavein-Dindo stage score and hospital stay were similar between patients with HBV DNA levels <500 copies/mL and patients with detectable HBV DNA levels (*P*=0.436 and *P*=0.934).

Then, we compared the postoperative complications between patients with PHR and patients without PHR and found that patients with PHR had a significantly higher morbidity rate (*P*=0.048) and a higher Clavein-Dindo stage score (*P*=0.038) (Table S1).

We also conducted univariate and multivariate analyses of HCC recurrence and found the following risk factors: HBeAg positivity (HR =5.36, 95% CI 1.523–18.863, *P*=0.009), portal vein thrombus (HR =1.70, 95% CI 0.227–3.135, *P*=0.047), and blood transfusion (HR =218.15, 95% CI 21.946–2,168.391, *P*<0.001) (Table S2).

Perioperative changes

Both biochemical (PT, TBil, ALB, ALT, and AFP) and immune ($CD3^+CD4^+$ and $CD3^+CD8^+$) outcomes were compared between patients with PHR and patients without PHR (Table S3). We found that patients with PHR had significantly lower ALB levels not only preoperatively (*P*=0.001) but also postoperatively (*P*=0.032). However, levels of PT, TBil, ALT, and AFP were similar between the two groups. Patients with PHR had a significantly lower percentage of $CD3^+CD4^+$ (*P*=0.041) at baseline and a significantly lower percentage of $CD3^+CD4^+$ (*P*<0.001) and $CD3^+CD8^+$ (*P*<0.001) after hepatectomy when compared with patients without PHR.

Literature review

A total of eight studies were enrolled in our review.[9–12,14,16,22,23] We analyzed the PHR, recurrence, RFS, and associated risk factors. Most patients were from Southeast Asia, which has the highest prevalence of HCC (Tables S4 and S5).

Table 3 Univariate and multivariate analyses of prognostic factors for recurrence-free survival in Chinese patients with HBV-related HCC

Factor	Univariate analysis				Multivariate analysis		
	Patients, n (%)	HR	95% confidence interval	*P*-value	HR	95% confidence interval	*P*-value
Postoperative HBV reactivation							
Yes	50 (19.4)	1.87	1.119–3.103	0.017	1.48	1.228–2.023	0.047
No	208 (80.6)						
Positive for HBeAg							
Yes	40 (15.5)	6.64	3.96–11.13	<0.001	4.84	2.617–8.941	<0.001
No	218 (84.5)						
Preoperative HBV DNA							
>500	99 (38.4)	10.30	5.110–20.777	<0.001	3.37	1.424–7.962	0.006
≤500	159 (61.6)						
Surgical margin (cm)							
>1.0	165 (64.0)	0.23	0.141–0.380	<0.001	0.53	0.290–0.964	0.038
≤1.0	93 (36.0)						
Hepatic inflow occlusion							
Yes	185 (71.7)	1.22	0.755–1.972	0.416	_	_	_
No	73 (28.3)						
Degree of liver cirrhosis							
Light (0–1)	151 (58.5)	2.41	1.500–3.878	<0.001	1.88	1.040–3.377	0.036
Moderate or more (≥2)	107 (41.5)						
Blood transfusion, n (%)							
Yes	51 (19.8)	6.40	3.938–10.404	<0.001	3.25	1.691–6.213	<0.001
No	207 (80.2)						

Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio.

Discussion

Many studies[9–11,14,16,22] and our previous study[13] figured out that PHR occurred after hepatectomy. However, the mechanism of PHR is not clear. We previously inferred that PHR may be associated with the immunosuppression induced by hepatectomy. Also, some other studies claimed that increased apoptosis of $CD4^+/CD8^+$ T-cells and the immunosuppression associated with surgical injury.[24,25] It is commonly believed that PHR remains the independent risk factor for HCC recurrence and RFS.[14,23] Moreover, studies found that preoperative antiviral therapy could efficiently decrease the PHR rate and reduce the HCC recurrence, thus prolonging the RFS.[14,16]

In our study, PHR rates are 3.0% and 21.8% in patients with and without antiviral therapy, respectively. The results were similar to those of our previous prospective study[13] (total PHR rate, 19.3%; PHR rate in patients with antiviral therapy, 2.2%; PHR rate in patients without antiviral therapy, 27.8%). In our literature review, total PHR rate varied from 6.1% to 40.7% and PHR rate varied from 0.0% to 4.7% in patients with antiviral therapy.[9–12,14,16,22,23] For patients with antiviral therapy, PHR rate was significantly decreased. Studies claimed that antiviral therapy predicted good long-term survival.[26,27] Other studies figured that antiviral therapy had no significant influence on HCC recurrence and OS.[28–30] Hepatocarcinogenesis may be initiated by continuous HBV replication.[31–33] Antiviral therapy may reduce HCC recurrence and prolong survival by suppressing and reducing continuous viremia and long-term hepatic inflammation. In our study, antiviral therapy remained the significant risk factor for PHR. However, antiviral therapy was not the independent risk factor for RFS and HCC recurrence. Also, we previously found that antiviral therapy failed to prolong short-term survival.[34]

PHR rate was lower in our study than that in the study conducted by Huang et al[14] (16.7%). It is mainly because the HBV DNA lower limit is different. Our lower limit was 500 copies/mL (1 IU/mL =1 copy/mL according to the instruction of the kit), whereas their lower limit was 200 IU/mL (800 copies/mL, 1 IU/mL =4 copies/mL according to Chinese guidelines[20]). In our result, HBV DNA load is still regarded as a risk factor, and a high HBV DNA load has been reported to be associated with an increased incidence of PHR.[14,35] In our literature review, antiviral therapy was found to be a protective factor.[9,11,12,14]

Due to the high incidence of HCC recurrence, OS of HCC patients still stays unsatisfied.[36] In our study, patients with PHR suffered worse RFS (RFS: 23 months and 29 months for patients with and without PHR, respectively, and 1-year, 2-year, and 3-year RFS rates were 75.8%, 38.1%, and 28.9% and 84.5%, 56.5%, and 40.7% for patients with and without PHR, respectively). As described by Huang et al,[14] PHR still remained the prognostic factor for RFS in multivariate regression analysis. Postoperative continuous HBV replication may constantly accelerate liver cirrhosis and give rise to HCC recurrence so as to decrease the RFS.[37,38] Continuously, viremia may do harm to our immune system and cause multicentric carcinogenesis.[39,40] Moreover, this replication may enhance tumor development and spread through the upregulation of adhesion molecules.[39]

We found that HBeAg positivity was the independent risk factor for HCC recurrence and OS. Many studies claimed that HBeAg-positive patients have a higher risk of PHR and are associated with HCC recurrence.[14,23] Also, a change from HBeAg-negative to HBeAg-positive status still related to PHR.[41,42] The immune system has been broken down in HCC patients, especially in postoperative HCC patients. Resection induces immunosuppression and permits enhanced viral replication. Therefore, patients in the immune clearance phase, especially HBeAg-positive patients, were at risk for reactivation of viral replication after surgery.

Several limitations could be found in this study. First, our retrospective design of the study was the biggest limitation. However, the baseline characteristics were similar between the two groups. This may decrease the selection bias to some extent. Second, we did not have long follow-ups, and we took only RFS into consideration. Ideally, we would continue to follow up on these patients for decades. In future, a better designed trial with a large sample and a long follow-up need to be further established.

Conclusion

PHR indeed occurs after hepatectomy in HBV-HCC patients. Antiviral therapy could efficiently decrease the incidence of PHR. Patients with PHR are associated with HCC recurrence and a worse RFS. Patients with HBV DNA levels $<$500 copies/mL still have the risk of PHR.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Postoperative complications between patients with and without PHR

Postoperative complications	Patients with PHR (n=50)	Patients without PHR (n=208)	*P*-value
Fever, n (%)	32 (64.0)	83 (39.9)	0.002
Nausea, vomiting, n (%)	5 (10.0)	18 (8.7)	0.764
Pain, n (%)	17 (34.0)	79 (38.0)	0.601
Liver function impairment, n (%)	39 (78.0)	129 (62.0)	0.033
Kidney function impairment, n (%)	4 (8.0)	27 (13.0)	0.468
Liver failure, n (%)	8 (16.0)	15 (7.2)	0.049
Bile leakage, n (%)	2 (4.0)	7 (3.4)	0.548
Gastrointestinal hemorrhage, n (%)	0 (0.0)	1 (0.5)	0.806
Infection, n (%)	11 (22.0)	21 (10.1)	0.022
Refractory ascites, n (%)	3 (6.0)	7 (3.4)	0.302
Pulmonary complication, n (%)	7 (14.0)	17 (8.2)	0.203
Postoperative fat liquefaction of incisions, n (%)	7 (14.0)	12 (5.8)	0.045
Urinary tract infection, n (%)	1 (2.0)	2 (1.0)	0.477
Pressure ulcers, n (%)	1 (2.0)	1 (0.5)	0.351
Clavein-Dindo stage score, mean ± SD	2.01±0.55	1.78±0.57	0.038
Overall incidence, n (%)	41 (82.0)	141 (67.8)	0.048

Abbreviations: HBV, hepatitis B virus; PHR, postoperative HBV reactivation; SD, standard deviation.

Table S2 Univariate and multivariate analyses of prognostic factors for HCC recurrence in Chinese patients with HBV-related HCC

Factor	Univariate analysis				Multivariate analysis		
	Patients, n (%)	HR	95% confidence interval	*P*-value	HR	95% confidence interval	*P*-value
Positive for HBeAg							
Yes	40 (15.5)	6.06	2.961–12.419	<0.001	5.36	1.523–18.863	0.009
No	218 (84.5)						
Portal vein thrombus, n (%)							
Yes	61 (23.6)	2.00	1.105–3.616	0.022	1.70	0.227–3.135	0.047
No	197 (76.4)						
Blood transfusion, n (%)							
Yes	51 (19.8)	64.05	23.319–175.904	<0.001	218.15	21.946–2,168.391	<0.001
No	207 (80.2)						

Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio.

Table S3 Perioperative changes in patients with HBV-related HCC

Index	Preoperative levels		*P*-value	Postoperative levels		*P*-value
	PHR (n=50)	Non-PHR (n=208)		PHR (n=50)	Non-PHR (n=208)	
PT (seconds)	13.51±1.64	12.73±1.41	0.876	13.91±1.57	13.61±1.67	0.821
TBil (μmol/L)	13.00 (6.50–16.70)	10.10 (4.50–14.20)	0.264	18.90 (11.30–22.50)	17.60 (9.80–20.60)	0.862
ALB (g/L)	36.01±2.27	41.32±4.79	0.001	31.75±5.79	36.10±4.26	0.032
ALT (IU/L)	38.30 (22.30–46.50)	34.10 (20.10–42.90)	0.291	130.50 (79.00–282.30)	115.20 (75.00–210.60)	0.086
AFP (ng/mL)	616.20 (8.00–12,100.00)	125.00 (6.50–12,100.00)	0.101	352.50 (6.30–4,940.00)	106.50 (4.50–3,630.00)	0.063
$CD3^+CD4^+$ (%)	31.17±8.83	38.46±8.71	0.041	18.94±7.14	39.97±11.02	<0.001
$CD3^+CD8^+$ (%)	21.34±7.28	22.39±7.55	0.621	13.74±5.49	25.43±7.46	<0.001

Note: Values are shown as mean ± SD, n (%), or average (range), unless otherwise indicated.
Abbreviations: AFP, α-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; PHR, postoperative HBV reactivation; PT, prothrombin time; TBil, total bilirubin.

Table S4 Characteristics and outcomes of recent literature and our study

Study	Country	Design	Patients, n	Antiviral therapy, n	PHR, n (%)			DFS	
					Total	Antiviral therapy	Nonantiviral therapy	PHR	Non-PHR
Dan et al[1]	People's Republic of China	Retrospective	93	35	13 (14.0)	1 (2.9)	12 (20.7)	–	–
Huang et al[2]	People's Republic of China	Retrospective	164	126	10 (6.1)	2 (1.6)	8 (21.2)	–	–
Huang et al[3]	People's Republic of China	Retrospective	1,609	150	308 (19.1)	7 (4.7)	301 (20.6)	3-year DFS: 34.1%	3-year DFS: 46.0%
Huang et al[4]	People's Republic of China	RCT	84	40	15 (17.9)	1 (2.5)	14 (31.8)	–	–
Huang et al[5]	People's Republic of China	Retrospective	1,602	227	175 (10.9)	4 (2.2)	170 (12.4)	–	–
Huang et al[6]	People's Republic of China	RCT	200	100	20 (10.0)	1 (1.0)	19 (19.0)	–	–
Lao et al[7]	People's Republic of China	Retrospective	204	83	19 (9.3)	0 (0.0)	19 (15.7)	–	–
Sohn et al[8]	Korea	Retrospective	130	64	53 (40.7)	–	–	–	–
Our study	People's Republic of China	Retrospective	258	33	50 (19.4)	1 (3.3)	49 (21.8)	1-year, 2-year, and 3-year DFS rate: 75.8%, 38.1%, and 28.9%, respectively	1-year, 2-year, and 3-year DFS rate: 84.5%, 56.5%, and 40.7%, respectively

Abbreviations: DFS, disease-free survival; HBV, hepatitis B virus; PHR, postoperative HBV reactivation.

Table S5 Prognostic factors of PHR, recurrence, and RFS in recent literature and our study

Study	Risk factors for PHR	Risk factors for HCC recurrence	Risk factors for RFS
Dan et al[1]	Without antiviral therapy and hepatic resection	–	–
Huang et al[2]	Without antiviral therapy and preoperative HBV DNA $<10^3$ copies/mL	–	–
Huang et al[3]	HBeAg positivity, HBV DNA level of ≥200 IU/mL, Ishak inflammation score of ≥3, preoperative TACE, operation time of >180 minutes, and blood transfusion	–	HBeAg positivity, HBV DNA level of ≥200 IU/mL, tumor diameter of >5 cm, presence of satellite nodules, presence of portal vein tumor thrombus, blood transfusion, resection margin of <1.0 cm, and HBV reactivation
Huang et al[6]	–	Tumor size of >5 cm, surgical margin of <1 cm, tumor encapsulation, presence of microsatellite nodules, and presence of microportal vein tumor thrombus	–
Lao et al[7]	Without antiviral therapy and hepatic inflow occlusion	–	–
Sohn et al[8]	Without antiviral therapy	HBeAg positivity, tumor number >1, microvascular invasion, and HBV reactivation	–
Our study	Without antiviral therapy, HBeAg positivity, HBV-cAg S1 positivity, preoperative HBV DNA level of ≥500 copies/mL, hepatic inflow occlusion, moderate liver cirrhosis or more, operating time >180 minutes, and blood transfusion	HBeAg positivity, tumor thrombus, and blood transfusion	PHR, HBeAg positivity, surgical margin <1 cm, moderate liver cirrhosis or more, and blood transfusion

Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HBV-cAg S1, against hepatitis B core antigen S1; HCC, hepatocellular carcinoma; PHR, postoperative HBV reactivation; RFS, recurrence-free survival; TACE, transarterial chemoembolization.

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