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Original Article

Hepatitis B virus DNA level predicts poor outcomes in hepatocellular carcinoma patients

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Abstract: Purpose: Adequate preoperative assessment plays an important role in achieving good postoperative outcomes, and chronic liver diseases induced by hepatitis B virus (HBV) infection are the major causative factor for hepatocellular carcinoma (HCC). Thus, this study was designed to investigate the effects of HBV DNA level on perioperative liver function and postoperative complications in HCC patients who underwent hepatectomy. Materials and Methods: Totally, 374 HCC patients with hepatectomy were included in this retrospective study. All the patients were divided into Group A (HBV DNA < 1.0E+04 IU/ml) and Group B (HBV DNA ≥ 1.0E+04 IU/ml). The changes of HBV-DNA level, liver function, complications and the length of hospital stay of patients were closely observed before operation and on postoperative days 1 (Day 1), 3 (Day 3) and 7 (Day 7). Univariate and multivariate analyses were also conducted for complications. Results: HBV-DNA level was significantly increased on Day 3 and Day 7 ($P < 0.05$). Statistical differences of ALT and AST activities were found between Group A and Group B on Day 1 ($P < 0.05$). Meanwhile, the length of hospital stay in Group B was significantly longer than that in Group A ($P < 0.05$). Postoperative complications, especially pulmonary infection and bile leakage, were more common in Group B ($P < 0.05$). Furthermore, high preoperative HBV DNA level was identified as an independent risk factor for postoperative complications. Conclusion: Preoperative HBV DNA level has significant influences on perioperative hepatic function and postoperative complications.

Keywords: Hepatocellular carcinoma, liver resection, hepatitis B virus (HBV)-DNA levels

Introduction

Hepatocellular carcinoma (HCC), one of the most common cancers, is considered as the third leading cause of cancer-related deaths worldwide [1]. Over the past 15 years, the incidence of HCC has increased more than double [2]. Currently, hepatectomy is considered as the preferred and effective treatment for HCC [3]. Although hepatectomy has obtained impressive growth in recent decades, the high risk rates of postoperative complications and recurrence remain the major concerns [4, 5]. The common postoperative complications after hepatectomy include pleural effusion, pneumonia, wound infection and biliary leakage [6]. Thus, it is necessary to search for effective methods to reduce the postoperative complications and avoid postoperative liver failure [7].

Preoperative evaluation of the liver function plays a critical role in reducing the postoperative complications of patients underwent hepatectomy [8]. Model for end-stage liver disease (MELD) score and Child-Pugh score can assess whole liver function, and they are useful in determining HCC patients as candidates for hepatectomy. Since Child-Pugh score is composite of several parameters, actual liver function may be different in patients with the same score [9]. In addition, MELD score seems to have a good performance in predicting acute kidney injury; however, its prognostic accuracy is still far from satisfactory [10]. Therefore, some new and accessorial preoperative indicators should be exploited for HCC patients to monitor liver function and reduce postoperative complications after hepatectomy. Recent studies have shown that the progression to HCC in

patients with chronic HBV infection is significantly associated with circulating HBV-DNA level [11, 12]. In addition, Huang *et al.* have demonstrated that preoperative HBV-DNA level more than 2.0E+04 IU/ml is one of the risk factors for postoperative liver failure in patients underwent hepatectomy [13]. However, the effects of HBV DNA level on the perioperative liver function and postoperative complications have not been fully elucidated, and it is still unclear whether a lower HBV DNA level can influence perioperative liver function and postoperative complications.

This study recruited a total of 374 patients who underwent hepatectomy in Affiliated Hospital of University of Electronic Science and Technology, and then investigated the effect of preoperative HBV-DNA level on perioperative liver function and postoperative complications.

Materials and methods

Subjects

The whole protocol of this study was approved by the Regional Ethics Committee of our hospital. Written informed consents for this study were obtained from the participants. A total of 613 HCC patients underwent hepatectomy from January 2008 to August 2013 in Affiliated Hospital of University of Electronic Science and Technology. The inclusion criteria were as follows: (1) patients were conformed with the HCC clinical diagnostic criteria and surgery indications defined by the guidelines on the diagnosis and treatment of primary liver cancer [13]; (2) patients were positive with hepatitis B surface antigen, but negative with HAV and HCV; (3) patients were generally in good condition without other serious illnesses (such as liver, kidney, lung, heart diseases) according to the preoperative examinations; (4) intraoperative blood loss was less than 1500 ml and blood transfusion was less than 800 ml [14, 15]; (5) they did not receive immunosuppressive therapy, antiretroviral therapy and chemotherapy before surgery; (6) preoperative Child-Pugh classification [16] was Class A or Class B; (7) solitary tumor was recorded and HCC was confirmed by postoperative pathological diagnosis; (8) other organs except for gallbladder did not undergo resection. As a result, a total of 374 HCC patients (312 males and 62 females; average age 50.92 ± 13.94 years) were included in this retrospective study.

In order to investigate the effects of the preoperative HBV DNA level on the perioperative liver function recovery, all the cases were classified into two groups: namely Group A (HBV DNA < 1.0E+04 IU/ml [17, 18]) including 135 males and 38 females and Group B (HBV DNA ≥ 1.0E+04 IU/ml) including 177 males and 24 females.

Surgical procedure

Supportive care was conducted in all the patients before operation, including the supplement of vitamin K, the improvement of hypoproteinemia and coagulation disorders. The range of surgical resection was determined depending on the results of magnetic resonance imaging and computed tomography. All the patients were anesthetized by intravenous injection of remifentanil and inhalation of sevoflurane. Resection standards were: (1) there were definite fibrous capsule or clear boundaries between the tumor and liver tissue, and no satellite nodule was found in liver cancer specimens; (2) the distance between foci and the cutting edge was more than 1 cm; and (3) the tumor invasion was not observed in the blood vessel and bile duct. Postoperative therapies were performed in all patients, including hepatoprotective drugs (polyene phosphatidylcholine, isoglycyrrhizinate magnesium and Ornithine aspartate), acid suppression, hemostasis, sufficient glucose, maintaining the balance of water and electrolyte, and improving immunity. If necessary, human serum albumin was supplied to maintain serum albumin level no less than 35 g/L.

Monitoring indicators

HBV DNA level, liver function indicators including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (TBIL) values, and the length of hospital stay were recorded preoperatively (pre) and/or on post-operative days 1 (Day 1), 3 (Day 3) and 7 (Day 7). The level of HBV DNA in blood was detected using SYBR green real-time quantitative reverse transcription-PCR (qRT-PCR). Routine liver biochemical tests were assessed using a sequential multiple auto analyzer (H-7600; Hitachi Ltd., Tokyo, Japan).

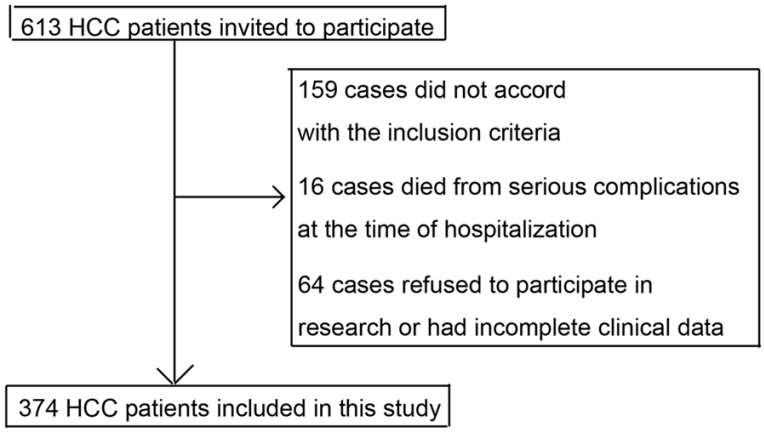

Figure 1. Flow chart depicting the recruitment process of patients in this study.

Postoperative complications

After hepatectomy, the complications, including abdominal bleeding, pleural effusion, pulmonary infection, abdominal infection, wound infection, bile leakage and HBV reactivation, were closely observed and recorded. The complications were defined as conditions or events which were unfavorable to patient's health and caused irreversible damage. Meanwhile, recurrent or progressive tumors occurred during the whole study were not regarded as treatment-related events. Patients with complications required a change in therapeutic policy and might need a prolongation of hospital stay. In this study, HBV reactivation was defined as a tenfold increase of HBV DNA level compared with the baseline HBV DNA level or the HBV DNA level became detectable from an undetectable baseline level. Pleural effusion was detected using X-ray examination and classified as follows: effusion hereinafter the fourth rib refers a small amount of pleural effusion; effusion between the fourth and the second ribs refers a moderate amount of pleural effusion; effusion above the second rib refers a serious pleural effusion.

Statistical analysis

All categorical variables were presented as frequency and analyzed using Pearson χ^2 test. The continuous variables were presented as mean ± standard deviation (SD) and the differences between Group A and Group B were analyzed using Student's *t* test. Meanwhile, paired T test was conducted for the differences of HBV DNA levels and liver function parameters before and after operation. Furthermore, univariate and multivariate logistic regression analysis were also performed to search the independent risk factors for postoperative complications. A value with $P < 0.05$ was considered as statistically significant difference. All statistical analyses were performed using the standard statistical package of SPSS 19.0 (IBM, Armonk, New York, USA).

Results

Characteristics of HCC patients

As shown in **Figure 1**, a total of 613 HCC patients underwent hepatectomy were invited to participate in this study. Among these patients, 239 patients were excluded in this study, including 159 cases who did not accord with the inclusion criteria, 16 cases who died from serious complications at the time of hospitalization, and 64 cases who refused to participate in research or had incomplete clinical data. As a result, a total of 374 HCC patients were included in this study. No significant differences were found in the preoperative situation (gender, age, liver function, Child-Pugh grade, tumor size, and whether combined with cirrhosis) and the intraoperative situation (anesthesia time, surgery time, hepatic portal occlusion, blood loss and surgical resection) of the patients between Group A and B (**Table 1**). However, postoperative hospital stay in Group B was significantly longer than that in Group A (17.12 ± 6.00 days vs. 10.09 ± 5.93 days, $P = 0.002$) (**Table 1**).

Perioperative difference of HBV DNA levels in the two groups

There were statistical differences of HBV DNA level between the Group A and B before and after operation ($P < 0.05$) (**Table 2**). Compared with the preoperative HBV DNA level, the HBV DNA level in Group A and B were both significantly increased on Day 3 and Day 7 ($P < 0.05$) (**Table 2**).

Table 1. Patient backgrounds and intraoperative parameters of the study groups

Variable	Group A (n = 173)	Group B (n = 201)	χ^2/F	*P*-value
Male/female	135/38	177/24	1.229	0.541
Age (years)	51.59 ± 13.69	49.20 ± 14.32	0.991	0.376
Child-Pugh classification (A/B)	101/72	115/86	0.702	0.704
Tumor diameter (cm)	5.75 ± 3.76	7.48 ± 4.68	1.742	0.183
Combined with cirrhosis	161	184	0.103	0.950
Preoperative ALT (U/L)	57.41 ± 41.36	66.00 ± 44.96	0.300	0.742
Preoperative AST (U/L)	63.04 ± 54.36	68.76 ± 30.48	0.170	0.844
Preoperative TBIL (mol/L)	21.83 ± 8.26	26.50 ± 35.74	0.528	0.592
Albumin (g/L)	40.47 ± 4.23	38.58 ± 3.74	1.370	0.261
Anesthesia time (min)	292.78 ±83.01	322.40 ± 105.03	1.020	0.366
Operative time (min)	253.15 ± 87.06	288.20 ± 91.47	1.333	0.270
Pringle case	152	193	2.865	0.239
Pringle blood time (min)	34.82 ± 17.56	21.25 ± 8.76	2.179	0.137
Operative blood loss (ml)	534.44 ± 331.31	658.00 ± 407.14	0.781	0.462
Blood transfusion volume (ml)	216.67 ± 306.03	356.00 ± 335.51	1.485	0.233
Length of postoperative hospital stay (days)	10.09 ± 5.93	17.12 ± 6.00	6.540	0.002

Group A: HBV DNA < 1.0E+04 IU/ml, Group B: HBV DNA ≥ 1.0E+04 IU/ml; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin. P < 0.05 represents significant difference analyzed using Student's t test or Pearson χ^2 test.

Table 2. Changes of HBV DNA levels

Category	Group A (n = 173)	Group B (n = 201)	χ^2/F	*P*-value
Preoperative level	3.82 ± 1.66E+03	6.25 ± 4.17E+05	5.271	0.031
Day 1	6.17 ± 5.83E+03	6.38 ± 2.15E+05	4.873	0.035
Day 3	5.48 ± 2.41E+04*	7.33 ± 3.84E+06*	8.479	0.026
Day 7	2.91 ± 1.54E+04*	4.15 ± 3.71E+06*	7.739	0.028

HBV: hepatitis B virus; Post-operative days 1 (Day 1), 3 (Day 3) and 7 (Day 7); *Significant differences (P < 0.05 vs. preoperative levels) analyzed using paired T test. Group A: HBV DNA < 1.0E+04 IU/ml, Group B: HBV DNA ≥ 1.0E+04 IU/ml; P < 0.05 represents significant difference analyzed using Student's t test.

Perioperative serum ALT, AST and TBIL levels in the two groups

Hepatocellular function damage was assessed via detecting the serum values of ALT, AST and TBIL. The changes of the perioperative serum ALT, AST and TBIL values are shown in **Figure 2**. As a result, the curves of the perioperative serum ALT, AST and TBIL values in Group B was higher than those in Group A (**Figure 2**). ALT and AST levels were rapidly increased to a peak on Day 1 and then returned to the baseline value on Day 7 (**Figure 2**). Compared with Group A, ALT and AST levels were significantly elevated in Group B on Day 1 ($P < 0.05$). Meanwhile, the TBIL level was elevated and at peak on Day 3, and then was down to preoperative levels on Day 7 (**Figure 2**). No significant difference was found in TBIL level between the two groups after operation ($P > 0.05$).

Postoperative complications in the two groups

Postoperative complications, including abdominal bleeding, pleural effusion, pulmonary infection, abdominal infection, wound infection and bile leakage, are listed in **Table 3**. Compared with Group A, the occurrence rates of pulmonary infection (18.9% vs. 5.2%, $P < 0.05$) and bile leakage (16.9% vs. 2.3%, $P < 0.05$) were remarkably increased in Group B. Meanwhile, the rate of HBV reactivation in group B was significantly higher than that in group A (64.2% vs. 48.0%, $P < 0.05$) (**Table 3**). Accordingly, the postoperative complications were significantly different between the two groups (84.1% vs. 51.4%, $P = 0.000$) (**Table 3**).

Univariate and multivariate analyses for postoperative complications

According to the univariate analysis results, Child-Pugh, preoperative HBV-DNA level and tumor diameter were associated with postoperative complications ($P < 0.05$, **Table 4**). However, gender, age, preoperative ALT, liver cirrhosis, hepatectomy, surgical time, hepatic portal occlusion and blood loss were unrelated

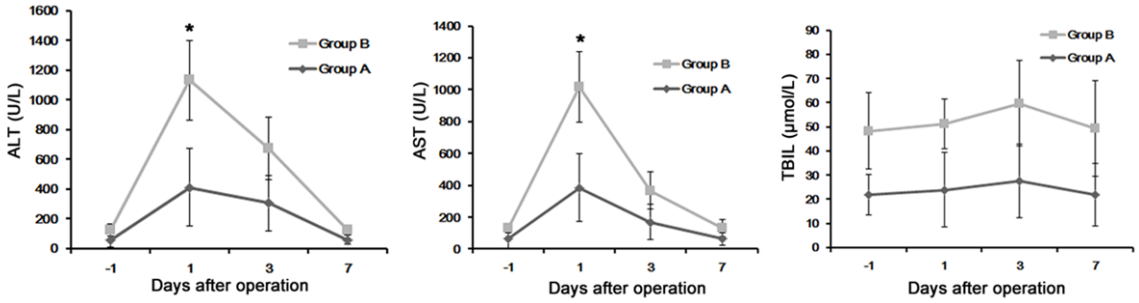

Figure 2. Perioperative changes of serum ALT, AST and TBIL values. The levels of ALT, AST and TBIL in serum were detected using ELISA assay. Group A: HBV DNA < 1.0E+04 IU/ml, Group B: HBV DNA ≥ 1.0E+04 IU/ml; Data are expressed as mean ± standard deviation (SD) the differences between Group A and Group B were analyzed using Student's t test, and the differences of HBV DNA levels and liver function parameters before and after surgery were analyzed using paired T test.

Table 3. Distribution of postoperative complications

Type of complication	Group A (n = 173)	Group B (n = 201)	χ^2/F	*P*-value
Abdominal bleeding	1 (0.5%)	3 (1.5%)	5.963	0.382
Pleural effusion	82 (47.4%)	154 (76.6%)	7.441	0.152
Pulmonary infection	9 (5.2%)	38 (18.9%)	11.385	0.041
Abdominal infection	2 (1.1%)	6 (3.0%)	3.649	0.581
Wound infection	12 (6.9%)	33 (16.4%)	4.125	0.416
Biliary leak	4 (2.3%)	34 (16.9%)	12.393	0.038
HBV reactivation	83 (48.0%)	129 (64.2%)	6.658	0.010
Total	89 (51.4%)	169 (84.1%)	56.013	0.000

Group A: HBV DNA < 1.0E+04 IU/ml, Group B: HBV DNA ≥ 1.0E+04 IU/ml; HBV: hepatitis B virus. P < 0.05 represents significant difference analyzed using Pearson χ^2 test.

to the incidences of postoperative complications (**Table 4**). Furthermore, based on the multivariate logistic regression analysis, Child-Pugh (*P* = 0.021, odds ratio [OR] 4.128, 95% confidence interval [CI] 1.336-8.479), preoperative HBV-DNA level (*P* = 0.027, OR 6.146, 95% CI 2.182-9.338) and tumor diameter (*P* = 0.041, OR 7.882, 95% CI 3.184-9.766) were considered as the independent risk factors for postoperative complications (*P* < 0.05, **Table 5**) in HCC patients underwent hepatectomy.

Discussion

The present study compared not only the perioperative liver function but also postoperative complications between low (HBV DNA < 1.0E+04 IU/ml) and high (HBV DNA ≥ 1.0E+04 IU/ml) HBV DNA level groups. The results showed that at the perioperative serum levels of ALT, AST and TBIL, postoperative complications and postoperative hospital stay length were all improved in low HBV DNA level group compared with those in high HBV DNA level group. Furthermore, preoperative HBV DNA level more than 1.0E+04 IU/ml was identified as an independent risk factor for postoperative complications.

HBV had no direct effect on the infected hepatocyte and it caused liver damage by triggering a protective immune response [19]. Previous study demonstrated that patients with hepatitis B were usually accompanied with the disorders of immune function caused by immunological injury [20]. HBV reactivation in lymphoma patients with chronic HBV infection was considered as a fatal complication of chemotherapy [21]. Yeo *et al.* certified that HBV reactivation occurred in 47% of lymphoma patients during chemotherapy process [22]. Yagci *et al.* reported the high risk of HBV reactivation in patients with chronic lymphocytic leukemia during chemotherapy process [23]. The reactivation rate of HBV was high in patients with high preoperative HBV-DNA level and these patients were more likely to be detected with liver failure and other serious complications after hepatectomy [13]. As the level of HBV-DNA was an independent predictor for the virologic response, and the early addition of drugs was critical for preventing the increase of HBV-DNA level [24]. In this study, the HBV-DNA level were significantly increased in both Groups A and B on Day 3 and Day 7. Consistent with the previous reports, the HBV reactivation was more common in patients

Table 4. Univariate analysis for complications

Factors	Complications		*OR*	*P*-value
	Yes (n = 258)	No (n = 116)		
Gender				
Male	217	95	0.889	0.623
Female	41	21		
Age				
> 40	39	12	1.983	0.216
≥ 40	219	104		
Child-Pugh				
A	124	92	2.967	0.041
B	137	21		
Preoperative HBV-DNA level (IU/mL)				
< 1.0E+04	89	84	3.214	0.038
≥ 1.0E+04	169	32		
Preoperative ALT (U/L)				
< 40	62	27	1.667	0.815
≥ 40	196	89		
Cirrhosis				
Yes	237	108	0.862	0.158
No	21	8		
Tumor diameter (cm)				
< 5	95	67	3.842	0.016
≥ 5	163	49		
Liver resection				
Regular removal	188	85	1.138	0.662
Irregular removal	70	31		
Operation time (min)				
< 240	136	63	2.151	0.324
≥ 240	122	53		
Hepatic portal occlusion				
Yes	230	105	1.468	0.730
No	28	11		
Blood loss (mL)				
< 500	69	32	0.983	0.285
≥ 500	189	84		

ALT: alanine aminotransferase; HBV: hepatitis B virus. P < 0.05 represents significant difference analyzed using univariate logistic regression analysis.

Table 5. Multivariate logistic regression analysis for complications

Factors	β	SE	Wald	*P*	OR with 95% CI
Child-Pugh	3.165	0.694	2.948	0.021	4.128 (1.336-8.479)
Preoperative HBV-DNA level	2.443	0.420	4.384	0.027	6.146 (2.182-9.338)
Tumor diameter	1.964	0.283	5.172	0.041	7.882 (3.184-9.766)

HBV: hepatitis B virus. P < 0.05 represents significant difference analyzed using multivariate logistic regression analysis.

with high preoperative HBV-DNA level than that in patients with low preoperative HBV-DNA level. A high HBV replication state was also identified as the greatest predictor for poor outcomes in HBV-related HCC patients after resection according to the study of An *et al.* in 188 patients [25]. All these results indicated that HCC patients with HBV infection were at risk of HBV reactivation after hepatectomy and antiviral therapy should be provided for the patients with high preoperative HBV-DNA levels before surgery.

As liver enzymes retained in hepatocytes, ALT and AST were well-known as surrogate parameters for hepatocyte injury or necrosis [26, 27]. Furthermore, recent study suggested that patients had high risks of postoperative complications if the perioperative serum activities of ALT and AST were in the upper range of normal [28]. Increasing evidences revealed a correlation between HBV-DNA level and serum ALT and AST activities [29]. As hepatotropic virus, HBV replication could not cause hepatocyte injury of host *in vivo*, while HBV reactivation could induce immune response, which indirectly resulted in hepatocyte injury [30]. Meanwhile, Huang *et al.* demonstrated that preoperative HBV DNA level more than 2.0E+04 IU/ml was a risk factor for postoperative liver failure in patients underwent hepatectomy [13]. In accordance with the previous finding, the serum ALT and AST activities were rapidly elevated on

Day 1 and were significantly higher in Group B than Group A on Day 1. This result suggested that the preoperative HBV DNA levels more than 1.0E+04 IU/ml might lead to more serious liver damage during surgery. To our limited knowledge, the immune response of the host hepatocyte caused by HBV antigen was considered as the main cause of hepatocyte injury [31]. With HBV DNA level increased, the immune injury was enhanced, which might lead to aggravated liver injury as well as increased ALT and AST activities [32]. Previous study reported that early administration of antiviral therapy could prevent the acute liver failure during liver transplantation [33]. Therefore, once HBV DNA level elevated, even if the change of ALT activities did not appear yet, antiviral therapy should be taken for the HCC patients to improve the liver function before hepatectomy.

Hepatectomy had been reported to be restricted by a relatively high rate of postoperative complications including pulmonary infection and bile leakage [34]. Pulmonary infection accounted for 20%-30% postoperative complications of hepatectomy and most commonly existed 3-5 d after operation. Pulmonary infection was considered as a high risk factor of pneumonia, which was common in immunodeficiency patients [35]. Biliary complications were also the common causes of major morbidity after hepatectomy. It had been reported that bile leakage might impair the normal defense mechanisms and make the patients predispose to sepsis, and finally lead to liver failure [36]. After hepatectomy, the incidences of pulmonary infection and bile leakage were more common in patients with high preoperative HBV DNA levels and without antiretroviral therapy according to previous studies [13, 37]. In this work, postoperative complications, especially pulmonary infection and bile leakage, were significantly increased in high preoperative HBV-DNA levels group compared with low preoperative HBV-DNA levels group. Consistent with the previous studies, hepatectomy might cause HBV reactivation, especially in the patients with high preoperative HBV DNA level [30, 38]. Besides, a high preoperative HBV DNA level was also certified as an independent risk factor for the postoperative complications. The underlying cause of the high rate of postoperative complications might be that HBV reactivation was more likely to occur among the patients with a high preoperative HBV DNA levels and HBV reactivation could seriously disrupt the body's immune response, which might lead to body more susceptible to be infected [39], and increase the risks of postoperative complications. Perioperative antiviral therapy had been suggested to improve the safety through reducing the incidences of postoperative complications and morbidity in patients with hepatitis B related HCC following hepatectomy [37]. Therefore, dominating the preoperative HBV-DNA level might contribute to reduce the postoperative complications and shorten the postoperative length of hospital stay for HCC patients underwent hepatectomy.

Our retrospective study still has several limitations. Firstly, multiple patient data were excluded due to incomplete information and unruly design. Meanwhile, the newer ways, such as Tc-Mebrofenin scan, should be conducted to quantify liver function preoperatively. Secondly, only the cases within 5 years and conditions during the hospitalization were investigated. In consideration of the complex relationship between the HBV DNA level and perioperative liver function, abundant studies with large population and long-term follow up are needed in future. Thirdly, the optimum cut-off of the HBV DNA level for antiretroviral therapy was also should be determined. Lastly, this study only showed that preoperative HBV DNA level had significant influences on perioperative hepatic function and postoperative complications, while the exact mechanisms should be investigated in the further study.

In conclusion, our study supported the speculation that the preoperative HBV-DNA level more than 1.0E+04 IU/ml had significant impacts on perioperative liver function and the incidence rates of postoperative complications in HCC patients after hepatectomy, which confirmed the necessity of antiviral therapy in HBV-related HCC patients. More preoperative treatment and management may lead to good outcomes for patients underwent hepatectomy.

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Disclosure of conflict of interest

None.

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