Correlation between Low-Level Viremia and Hepatitis B-Related Hepatocellular Carcinoma and Recurrence: A Retrospective Study

Furong Sun
The First Hospital of China Medical University: The First Affiliated Hospital of China Medical University
https://orcid.org/0000-0002-9770-4789
Zhifei Liu
China Medical University
Bingyuan Wang (wangby0908@163.com)
https://orcid.org/0000-0002-4233-6093

Research article

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Abstract

Background

Low-level viremia generally refers to detectable HBV DNA levels lower than 2,000 IU/mL. Studies show that low-level viremia is a risk factor for hepatocellular carcinoma. The aim of this study was to explore the characteristics of low-level viremia patients with hepatitis B-related hepatocellular carcinoma and identify patient prognostic factors following curative hepatectomy.

Methods

Data from chronic hepatitis B patients with hepatocellular carcinoma receiving curative hepatectomy for the first time in the first hospital of China Medical University were studied. Patients were divided into two groups based on preoperative HBV DNA levels: group 1 (low-level viremia group, HBV DNA < 2,000 IU/mL) and group 2 (HBV DNA ≥ 2,000 IU/mL).

Results

Of the 212 patients, 104 patients were in group 1 and 108 patients were in group 2. There was a lower proportion of patients with HBsAg levels > 250 IU/mL in group 1 than in group 2 (71.2% vs. 86.1%, $P < 0.01$). The proportion of patients with a tumor diameter < 5 cm was 67.3% in group 1 and 37.0% in group 2 ($P < 0.000$). Tumor recurrence was 40.4% (42) in group 1 and 54.6% (59) in group 2 ($P < 0.05$). Median recurrence-free survival was 30.1 months in group 1 and 17.6 months in group 2 ($P < 0.01$). Multivariate analysis showed that a tumor diameter > 5 cm (hazard ratio [HR] = 1.819, 95% confidence interval [CI] 1.193–2.775, $P = 0.005$), intrahepatic metastasis (HR = 1.916, 95% CI 1.077–3.407, $P = 0.027$), and an HBV DNA level > 100 IU/mL (HR = 2.943, 95% CI 1.916–4.520, $P < 0.000$) were independent prognostic factors associated with an increased risk of hepatocellular carcinoma recurrence.

Conclusion

Preoperative low-level viremia was related to a long tumor recurrence interval and post-operative virologic response was associated with a lower risk of hepatocellular carcinoma recurrence.

Background

Hepatitis B viral (HBV) infection remains a serious global public health problem. HBV infection is the leading cause of hepatocellular carcinoma (HCC) worldwide, accounting for 33% of cases[1]. In China, chronic hepatitis B (CHB) contributes to approximately 84% of HCC[2]. The incidence of HBV-related deaths due to liver cirrhosis and/or HCC dramatically increased between 1990 and 2013[3], resulting in a large health and economic burden. Therefore, effective control of CHB is crucial. Serum HBV DNA level is

essential for informing decision-making regarding antiviral treatment and the subsequent monitoring of disease progression. A prospective cohort study showed that an HBV DNA level more than 10,000 copies/mL was a strong predictor of HCC development[4]. Long-term, maintained virologic response (VR) is associated with progression, even in those with decompensated liver cirrhosis[5].

Low-level viremia (LLV) can be detected in CHB patients including those taking antiviral therapy, generally referring to detectable HBV DNA levels lower than 2,000 IU/mL. Recently, an increasing number of studies have shown that LLV plays a crucial role in the diagnosis and prognosis of HCC. It has been reported that LLV is associated with a higher risk of HCC and poorer overall survival, compared with those who maintained VR[6, 7]. LLV patients with a relatively low viral load can still can benefit from effective antiviral therapy. One study showed that the risk of HCC was significantly decreased when LLV patients received antiviral therapy[7]. More importantly, antiviral therapy significantly reduced HCC recurrence after R0 hepatic resection[8].

Although the exact incidence of LLV is not known, the potential LLV population is likely considerable. Therefore, these patients should be included in routine follow-up as patients with a high-level viral load. During follow-up, continuous monitoring of cirrhosis and HCC is quite important. The strategy of antiviral therapy for LLV patients depends on several factors such as age, liver injury, liver cirrhosis, HBeAg, and HCC. The timing of antiviral therapy for LLV is controversial. Generally, LLV without liver cirrhosis or elevated ALT is considered inactive CHB, and is not an indication for antiviral therapy[2, 9]. However, due to the risk for HCC and because antiviral therapy could reduce HCC recurrence, it may be necessary for LLV patients to receive antiviral therapy at an earlier CHB stage and to maintain a long-term VR and undetectable HBV DNA.

Characteristics of CHB have been well described, and studies have revealed common characteristics of LLV. However, an overall understanding of LLV is lacking. Thus, there is still an urgent need to describe LLV characteristics and distinguish LLV patients from other CHB patients. This would help inform suitable management strategies for LLV patients and improve early detection of HCC. In this study, we explored the characteristics of LLV in HCC patients who had undergone partial hepatectomy. Then, prognostic factors were further analyzed in an effort to understand the differential characteristics of LLV patients versus those with a high-level viral load.

Methods

Study population

We obtained data on CHB patients who had been diagnosed with malignant liver tumors and underwent partial hepatectomy by open or laparoscopic hepatectomy in the first hospital of China Medical University between November 2011 and December 2018. Diagnosis of HCC was based on two types of imaging examinations including liver ultrasound, computed tomography, and magnetic resonance imaging. Diagnosis was further confirmed via analysis of resected specimens.

Inclusion criteria included: (1) first time hepatectomy for HCC, (2) history of CHB with positive hepatitis B surface antigen (HBsAg), (3) no extrahepatic metastasis, and (4) above 18 years old. Exclusion criteria included: (1) data incomplete, (2) history of hepatectomy for liver malignant tumors, (3) history of transcatheter arterial chemoembolization, (4) history of chemotherapy for HCC, (5) special types of HCC confirmed by resected specimens, (6) a combination of HCC and cholangiocarcinoma, (7) positive hepatitis C surface antibody, (8) secondary malignant tumor of the liver. Detailed patient information is shown in Fig. 1. The study was approved by institutional review board of our hospital and informed consent was obtained from all patients to use data from their medical records.

Preoperative Data

All patients were divided into two groups based on their preoperative serum HBV DNA levels: Group 1 included patients with serum HBV DNA levels less than 2,000 IU/mL, Group 2 included patients with serum HBV DNA levels ≥ 2,000 IU/mL.

Medical records were collected and included sex, age, history of antiviral therapy, smoking, and alcohol consumption. An alcohol consumption less than 30 g/d for males and 20 g/d for females was defined as moderate alcohol consumption; and an alcohol consumption more than 60 g on one occasion was defined as heavy episodic drinking[10]. Characteristics of liver tumors were carefully recorded, including the number of nodules, the maximum diameter, differentiation, capsule formation, intrahepatic metastasis, satellite nodules, and portal vein tumor thrombosis.

Blood samples were taken after an overnight fasting. Parameters including leukocyte count, hemoglobin, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), serum albumin (ALB), prothrombin time (PT), international normalized ratio (INR), creatinine, alpha-fetoprotein (AFP), HBsAg (upper limit of detection was 250 IU/mL in our laboratory), serum HBV DNA, and hepatitis B e antigen (HBeAg) were then evaluated. Data from preoperative ultrasound, computed tomography, and/or magnetic resonance imaging were also collected.

Follow-up And Assessment Of Recurrence

All patients were followed-up once every month or 3 months in the outpatient department. Patients with detectable postoperative HBV DNA and liver cirrhosis were given antiviral therapy. Maintained VR was defined as persistent HBV DNA levels less than 100 IU/mL, the lower limit of detection in our laboratory, during follow-up. Blood samples were taken after an overnight fasting for analysis of liver function, AFP, and HBV DNA levels at every visit. Liver ultrasound, computed tomography, and/or magnetic resonance imaging were taken at the same time to monitor for new lesions in the liver.

Tumor recurrence was defined as (1) new lesions in the liver suspected by liver ultrasound and furthered confirmed by computed tomography or magnetic resonance imaging with or without elevated serum AFP;

(2) new lesions in the liver detected by liver ultrasound, computed tomography, or magnetic resonance imaging, and further confirmed in resected specimens.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range). Quantitative variables were compared by Student's *t* test for continuous variables with a normal distribution or the Mann-Whitney nonparametric *U* test. Categorical variables were analyzed by Chi-square test and are expressed as numbers and percentages. Recurrence-free survival was calculated by the Kaplan-Meier method and the differences were compared by log-rank test. Univariate and multivariate analyses were performed by the Cox proportional hazards regression model with stepwise selection of variables. Statistical analysis was performed using IBM SPSS statistics software version 22.0 (IBM, Armonk, NY, USA) A *P* value < 0.05 was considered statistically significant.

Results

Characteristics of patients

A total of 169 males and 43 females were enrolled in the study; 104 patients were in group 1 and 108 patients were in group 2. The mean age was 54.5 ± 9.6 years, ranging from 23 to 81 years old. The percentage of patients with a history of smoking or alcohol consumption was 18.4% and 14.2%, respectively. There were no significant differences in sex, age, history of smoking, and alcohol consumption between the two groups ($P > 0.05$). Details are shown in Table 1.

A total of 167 (78.8%) patients demonstrated a serum HBsAg level > 250 IU/mL, and there were 28.8% patients with positive HBeAg. There was a lower proportion of patients with HBsAg levels greater than 250 IU/mL in group 1 than in group 2 (71.2% vs. 86.1%, $P < 0.01$). The proportion of patients with positive HBeAg was much higher in group 2 than in group 1 (39.8% vs. 17.3%, $P < 0.000$). Details are shown in Table 1.

Tumor Characteristics

Liver cirrhosis was observed in most enrolled CHB patients, with a percentage of 75.0% in group 1 and 82.4% in group 2 ($P > 0.05$). The percentage of well, moderate, and poor differentiation was 19.3% (39), 64.4% (130), and 16.3% (33), respectively ($P > 0.05$). Capsule was observed in 61.3% (130) of cases, the percentage of tumors with capsule formation was 52.9% in group 1 and 69.4% in group 2 ($P < 0.05$). The percentage of patients with a tumor diameter less than 5 cm was 67.3% in group 1 and 37.0% in group 2 ($P < 0.000$). Details are shown in Table 1.

Preoperative Laboratory Tests

Routine blood tests showed that the mean leukocyte count, platelet count, and hemoglobin were in the normal ranges with no significant difference between groups ($P > 0.05$). Similarly, the mean PT and INR

was normal ($P > 0.05$). Mean ALP and median ALT, AST, and GGT was higher in group 2 than in group 1 ($P = 0.02$ for ALP, $P < 0.000$ for ALT, AST, and GGT). The mean ALB was lower in group 2 than in group 1 (38.8 ± 3.7 vs. 41.5 ± 3.5, $P < 0.000$). Median serum AFP concentration was 69.57 ng/mL for all patients; a much higher median AFP level was observed in group 2 patients (145.50 vs. 23.09, $P < 0.01$). A total of 41 (39.4%) patients in group 1 and 24 (22.2%) patients in group 2 had an AFP level under 10 ng/mL ($P < 0.01$). Details are shown in Table 1.

Follow-up

The median follow-up was 13.5 months. At the end of follow-up, a total of 101 (47.6%) patients experienced HCC recurrence, 42 (40.4%) in group 1 and 59 (54.6%) in group 2. The difference between groups was significant ($P < 0.05$). A total of 80 patients (76.9%) in group 1 had a persistent serum HBV DNA level less than 100 IU/mL at follow-up, while the number was 48 (44.4%) in group 2 ($P < 0.000$). Details are shown in Table 1.

Median recurrence-free survival was 30.1 months in group 1 and 17.6 months in group 2 (log-rank $P = 0.015$, $P < 0.01$) (Fig. 2). When comparing patients with a serum HBV DNA more than 100 IU/mL at the end of follow-up, patients that maintained a serum HBV DNA level less than 100 IU/mL exhibited a longer recurrence-free survival (40.8 vs. 11.4, $P < 0.000$). Details are shown in Table 1.

Parameters significantly associated with hepatocellular recurrence on univariate analysis were then used for multivariate analysis. Analysis showed that a tumor diameter more than 5 cm (hazard ratio [HR] = 1.819, 95% confidence interval [CI] 1.193–2.775, $P = 0.005$), intrahepatic metastasis (HR = 1.916, 95% CI 1.077–3.407, $P = 0.027$), and an HBV DNA level > 100 IU/mL (HR = 2.943, 95% CI 1.916–4.520, $P < 0.000$) were independent prognostic factors associated with an increased risk of HCC recurrence. Details are shown in Table 2.

Discussion

HBV DNA levels are an important indicator of CHB at different stages. In this study, differences in preoperative and post-operative HBV DNA levels between two groups demonstrated that maintained VR was associated with longer recurrence-free survival, especially for LLV patients. Compared to patients with preoperative HBV DNA ≥ 2,000 IU/mL, median recurrence-free survival was much longer in LLV patients. Univariate analysis showed that preoperative HBV DNA levels ≥ 2,000 IU/mL were a prognostic factor for tumor recurrence risk (HR 1.629, 95%CI 1.095–2.423, $P = 0.016$), but this result was not confirmed by multivariate analysis ($P = 0.976$) in this cohort. However, multivariate analysis demonstrated that a post-operative serum HBV DNA level > 100 IU/mL was an independent prognostic factor of an increased risk of HCC recurrence after curative hepatectomy. Similarly, a prospective study showed that post-operative antiviral treatment improved survival in LLV patients, especially long-term survival[8]. Taken together, these data suggest that maintained VR in CHB patients after curative hepatectomy may dramatically improve tumor recurrence-free survival.

Serum HBsAg level is an important characteristic of CHB that is useful for identifying the stage of disease and can affect nucleos(t)ide analogue therapy[11, 12]. More importantly, HBsAg levels are associated with the risk of progression to HCC, especially in LLV patients with negative HBeAg[13]. The natural course of HBsAg level is different from HBV DNA, HBsAg declines very slowly in most cases over time[14]. In this cohort, the percentage of patients with a serum HBsAg concentration greater than 250 IU/mL was high in both LLV patients and patients with HBV DNA ≥ 2,000 IU/mL (71.2% and 86.1%, respectively). Studies have shown that serum HBsAg levels may reflect the amount and transcriptional activity of covalently closed circular DNA, the transcriptional template for the virus, inside the hepatocyte [15]. Therefore, LLV or undetectable HBV DNA does not necessarily indicate progress control. Consequently, a more exact quantitative HBsAg level, not a detection upper limit of 250 IU/mL, is urgently needed for the assessment of antiviral therapy during follow-up.

Although LLV patients may benefit from a low HBV DNA load, LLV is still a risk factor for HCC recurrence[6]. A low level of residual HBV (20–200 IU/mL) may still promote fibrotic progression in CHB patients during antiviral therapy[16]. For most patients, VR can be achieved after antiviral therapy. As we have shown, the percentage of patients with post-operative HBV DNA levels less than 100 IU/mL was 76.9% in LLV patients and 44.4% in patients with HBV DNA ≥ 2,000 IU/mL. Therefore, LLV patients may be more prone to developing and maintaining VR. Successive monitoring of HBsAg level is an important indicator for assessing disease progression, especially for those with undetectable HBV DNA. HBsAg clearance may be a second target for antiviral therapy in LLV patients. Serum HBsAg levels less than 100 IU/mL may indicate a high probability of spontaneous HBsAg clearance[15].

The main difference in tumor characteristics between the two groups was tumor diameter. It has been proven that tumor size is an important prognostic factor in HCC patients[17]. As demonstrated, 70 (67.3%) LLV patients had a tumor diameter less than 5 cm, while the number was 40 (37.0%) in patients with HBV DNA ≥ 2,000 IU/mL. Multivariate analysis verified that a tumor diameter > 5 cm was an independent prognostic factor for recurrence of HCC after curative hepatectomy (HR 1.819, 95% CI 1.193–2.775, $P = 0.005$). Tumor capsule formation is another important prognostic factor of HCC. There was a lower proportion of tumor capsule formation in the LLV patients than in patients in the other group (52.9% vs. 69.4%, $P < 0.01$). Univariate analysis showed that tumor capsule formation was not a prognostic factor. On the contrary, metastasis was an independent prognostic factor for HCC recurrence, as shown by multivariate analysis, as patients with intrahepatic metastasis had a higher risk of HCC recurrence (HR 1.916, 95% CI 1.077–3.407, $P = 0.027$). These results demonstrated that LLV patients with small tumors and without intrahepatic metastasis had a lower risk of tumor recurrence compared with patients with a high viral load. However, more studies are needed to confirm this.

Changes in liver enzymes reflect liver injury. Laboratory tests showed more serious liver injury in high-level viral load patients than in LLV patients. GGT levels were considered a predictor of early post-operative recurrence in a cohort of HBV-related HCC[18]. In this cohort, the preoperative median GGT level was much higher in group 2 than in group 1, and higher than the upper limit of normal. Serum ALT levels are an important indicator of hepatocyte damage and a predictor of long-term outcomes that may be used to

inform antiviral treatment decisions as well as treatment response[2, 9, 19]. We detected much higher serum ALT levels in group 2 than in group 1 (40 vs. 25, $P < 0.000$). Liver injury can be caused by many factors. First, HBV is a member of the hepadnaviridae family, and chronic viral activity causes sustained hepatocyte damage and release of ALT. High-level viral loads are more likely to cause serious liver injury. Second, tumor size is related to liver injury. A large tumor may impinge on normal liver tissues and lead to significant hepatocyte injury. As we have shown, the percentage of patients with a tumor diameter > 5 cm was 63% in patients with HBV DNA ≥ 2,000 IU/mL. These are likely the main reasons for more severe liver injury in patients with HBV DNA ≥ 2,000 IU/mL. However, elevated liver enzymes can be caused by other factors such as alcohol-associated liver disease, drug-induced liver injury, and metabolism-associated fatty liver disease. Nevertheless, medical history and resection specimen analysis indicated no obvious differences between the two groups.

AFP is useful for diagnosing and evaluating the recurrence of HCC. It has been shown that persistently elevated serum AFP levels are a risk factor for HCC development, especially for those with chronic liver disease. However, the usage of AFP in diagnosing HCC is controversial. A cutoff value of 20 ng/mL shows high sensitivity but low specificity, whereas a high cutoff value at 200 ng/mL lowers sensitivity dramatically[20], leading to a non-negligible risk of misdiagnosis. Importantly, active hepatitis may be a confounding factor in CHB patients. Patients with active CHB may show elevated AFP levels (> 20 ng/mL) before antiviral therapy and decreased AFP levels after antiviral therapy[21]. In this cohort, the percentage of preoperative AFP levels less than 10 ng/mL was 39.4% in LLV patients and 22.2% in patients with HBV DNA ≥ 2,000 IU/mL ($P < 0.01$). At the end of follow-up, the proportion of patients with AFP levels less than 10 ng/mL was similar in the two groups. Univariate analysis showed that a preoperative AFP concentration > 10 ng/mL was a risk factor for HCC recurrence, but this was not further verified by multivariate analysis. However, this suggests that screening for the risk of HCC in LLV patients should be carefully considered. Low AFP levels are not enough to exclude HCC and tumor recurrence. A dynamic monitoring of AFP and a combination of imaging data at follow-up are equally important.

There were some limitations in this study. First, metabolism-related fatty liver disease is gradually becoming an important risk factor for HCC. Data on body weight and height were missing in some patients, therefore body mass index could not be calculated and compared between groups. Second, the follow-up time was not long enough in some patients. All these factors should be further studied.

Conclusions

LLV is common in CHB patients with HCC. LLV patients should not be ignored, even before HCC or liver cirrhosis is diagnosed. A more suitable management strategy should be established to reduce the incidence of HCC in these patients. Antiviral therapy may be necessary for LLV patients. HBsAg levels could be an important indicator for monitoring the effects of antiviral therapy, aside from HBV DNA levels. LLV patients with HCC were characterized by smaller tumor size, less serious liver injury, and lower AFP levels compared to patients with HBV DNA ≥ 2,000 IU/mL. Preoperative LLV was related to a long tumor recurrence interval, and post-operative VR was associated with a lower risk of HCC recurrence.

Abbreviations

ALT: alanine aminotransferase
ALB: albumin
ALP: alkaline phosphatase
AFP: alpha-fetoprotein
AST: aspartate aminotransferase
CHB: chronic hepatitis B
CI: confidence interval
GGT: γ-glutamyl transpeptidase
HR: hazard ratio
HBeAg: hepatitis B e antigen
HBsAg: hepatitis B surface antigen
HBV: hepatitis B viral
HCC: hepatocellular carcinoma
INR: international normalized ratio
LLV: low-level viremia
PT: prothrombin time
VR: virologic response

Declarations

Ethical approval and consent to participate:

An Ethics Committee's approval is unnecessary for this manuscript in our hospital's rule because of its retrospective case study.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Funding:

Not applicable.

Authors' contributions:

FR Sun collected data and drafted the manuscript. ZF Liu collected and analyzed data, BY Wang designed the work and revised the manuscript. All authors have read and approved the manuscript.

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Tables

Due to technical limitations, table 1 and table 2 is only available as a download in the Supplemental Files section.

Figures

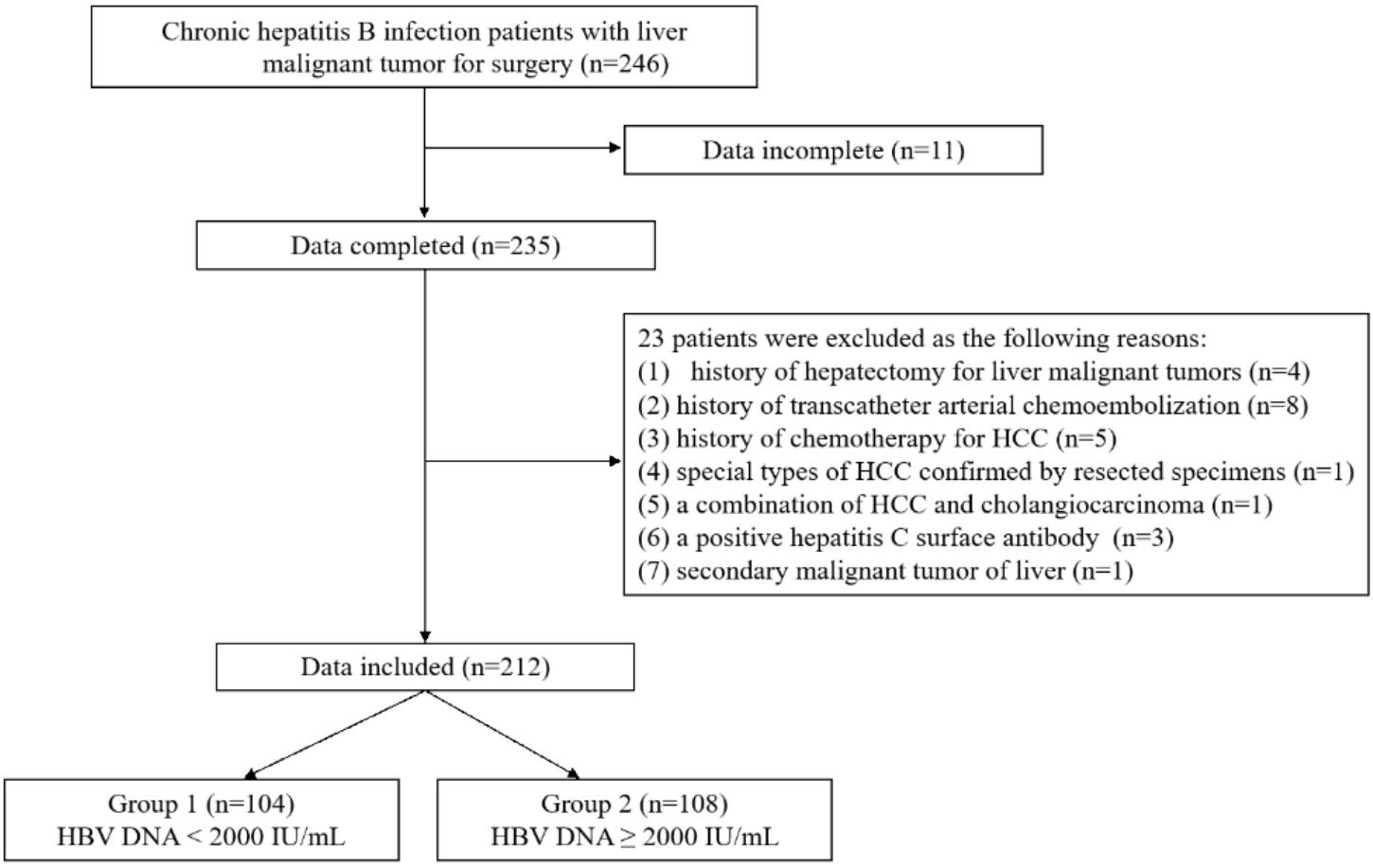

Figure 1

Flowchart of patients. HCC: hepatocellular carcinoma

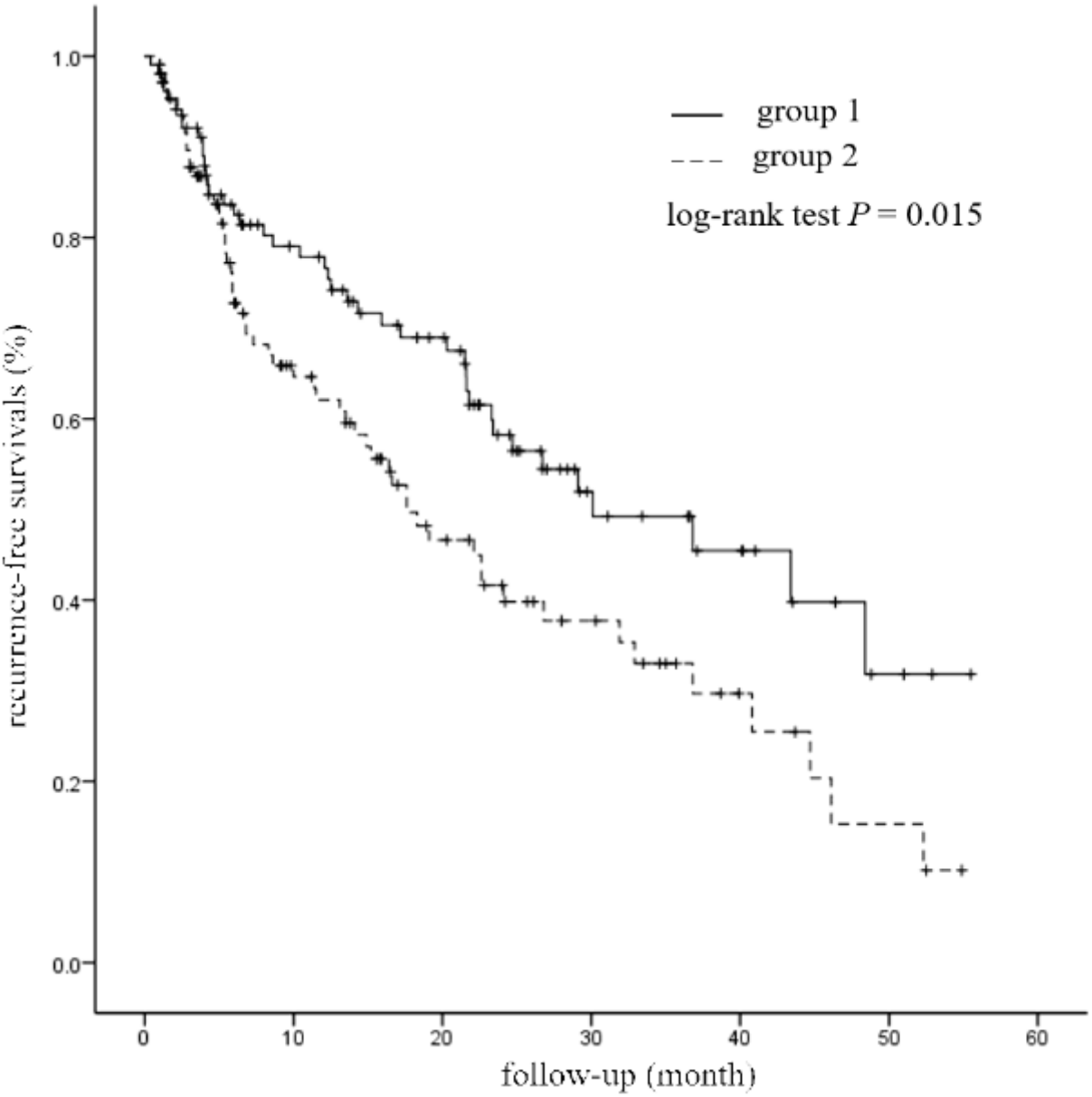

Figure 2

Comparison of tumor recurrence-free survival between the 2 groups. Kaplan-Meier curve of tumor recurrence-free survival based on preoperative HBV DNA levels. The median tumor recurrence-free survival was 30.1 months in group 1 and 17.6 months in group 2 (P < 0.01) (log-rank P = 0.015).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- table1.characteristicsofpatientsandtumors.tif
- table2.UnivariateandMultivariateAnalysesforRecurrence.tif