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**RESEARCH**                                                                                    **Open Access**

# Antiviral therapy predicts the outcomes following resection of hepatocellular carcinoma in patients negative for HBV DNA: a propensity score matching analysis

Mingxing Xu[1†], Zheng Zhou[2†], Ruiyun Xu[1], Huiling Zhang[1], Nan Lin[1*] and Yuesi Zhong[1*]

## Abstract

**Background:** The effect of antiviral therapy (AVT) on clinical outcomes in patients with hepatocellular carcinoma (HCC) who are seronegative for hepatitis B virus (HBV), defined as HBV DNA < 100 IU/ml prior to surgical resection, is unknown. The main purpose of this study was to evaluate the possible value of AVT in this cohort of patients.

**Methods:** From January 2006 to January 2013, 161 HCC patients with positive serum tests for HBV surface antigen (HBsAg) but negative tests for HBV DNA who had undergone hepatectomy were included and analyzed. Propensity score matching (PSM) was used to balance the heterogeneity in baseline characteristics.

**Results:** All patients were divided into the following two groups: the AVT group (n = 73, 45.34%) and the non-AVT group (n = 88, 54.66%). HBV reactivation occurred in 20 patients in the non-AVT group (22.73%) but in only 2 patients in the AVT group (2.74%, p < 0.001). After PSM, the 1-, 2-, and 3-year recurrence-free survival (RFS) rates in the AVT group and the non-AVT group were 78.38%, 72.97%, and 62.16% and 81.08%, 72.97%, and 72.97%, respectively (p = 0.564); the 1-, 2-, and 3-year overall survival (OS) rates were 97.30%, 97.3%, and 91.89% and 94.59%, 94.59%, and 86.49% in the AVT group and non-AVT group, respectively (p = 0.447).

**Conclusions:** Antiviral therapy can reduce HBV reactivation but is not correlated with a significant increase in postoperative RFS and OS in HCC patients with HBV DNA levels < 100 IU/ml.

**Keywords:** Antiviral therapy, Negative HBV DNA, Hepatocellular carcinoma, Survival

## Background

With introduction and uptake of the vaccine, hepatitis B virus (HBV) infection rate has not been increasing at the same rate; however, the large population of infected individuals renders the situation less optimistic. Two billion people worldwide have been infected with HBV, the most common pathogen that causes human viral hepatitis, and 250 million are chronically infected [1, 2]. HBV infection is the most common etiological factor leading to hepatocarcinogenesis, disproportionately affecting Asian countries. Globally, the proportion of patients with hepatocellular

carcinoma (HCC) caused by HBV infection is 45%, and in China, this proportion has reached approximately 80% [3, 4]. Hepatitis B and its complications, such as cirrhosis or HCC, have contributed to the burden healthcare places on society [5, 6]. Thus, the treatment of chronic hepatitis B patients is particularly important. Antiviral therapy (AVT) is regarded as the most effective treatment. It is expected that AVT can benefit patients with a persistent virological response (VR) [7–9]. Furthermore, AVT can reduce the risk of postoperative recurrence by reducing viral load in HBV-related HCC patients [10]. A recent study also confirmed that AVT is associated with reduced incidences of microvascular invasion (MVI) and early tumor recurrence after partial hepatectomy for HBV-related HCC patients [11]. To improve the prognosis of patients, most major guidelines have recommended AVT as one of the important treatments for HCC patients

* Correspondence: linn@mail.sysu.edu.cn; zhongyues@163.com
†Mingxing Xu and Zheng Zhou contributed equally to this work.
[1]Department of Hepatobiliary Surgery, The Third Affiliated Hospital of Sun Yat-Sen University, No. 600 Tianhe Road, Guangzhou 510630, Guangdong, China
Full list of author information is available at the end of the article

who test positive for HBV DNA during the perioperative period [12–14]. Previous studies have indicated that AVT can reduce the risk of virus reactivation, help improve liver function in patients with low levels of HBV DNA (HBV DNA < 500 IU/ml) after HCC surgery [15], and reduce HCC recurrence in patients with low HBV DNA levels (HBV DNA < 2000 IU/ml) [16]. However, whether AVT is useful in HCC patients who test negative for HBV DNA (HBV DNA < 100 IU/ml) to improve their clinical outcomes is still unknown, as evidence is lacking.

The present study evaluated the rate of post-hepatectomy HBV reactivation in HBV DNA-negative patients and explored the potential value of AVT for improving patient survival; the hypothesis was that AVT would be beneficial for HBV DNA-negative HCC patients (HBV DNA < 100 IU/ml).

## Materials and methods

All patients in this study provided written informed consent before undergoing operation. All procedures in this study were performed in accordance with the principles of the Research Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University and the Helsinki Declaration and its amendments. The study was reported in accordance with the STROCCS criteria [17].

### Study design and patient grouping

We retrospectively collected and analyzed the data of HCC patients who underwent hepatectomy in our institution between January 2006 and January 2013. Patients who met the following inclusion criteria were enrolled in this study: (a) the patient's hepatectomy was performed in our center, and HCC was pathologically confirmed after the operation; (b) the patient was positive for serum HBsAg before the surgery; (c) the patient's serum HBV DNA level was < 100 IU/ml; (d) the patient's liver function was Child-Pugh grade A or B; (e) if the patient received entecavir therapy, it was administered within 1 week before and after the hepatectomy; and (f) if the patient received entecavir (0.5 mg/d), they took it for at least 1 year after surgery.

Patients were excluded if they met one or more of the following exclusion criteria: (a) the patient received treatment that might affect their prognosis before surgery such as transcatheter arterial chemoembolization (TACE) or radiation therapy; (b) the patient had other tumors in other organs, for example, renal cell carcinoma and cervical cancer, or certain severe diseases; (c) the patient had refractory ascites or hepatic encephalopathy; (d) the patient had a positive resection margin (R1 resection); or (e) they had previously received any antiviral treatment.

### Definition of negative HBV DNA, reactivation, PVI, HVI, and MVI

In this study, we defined a negative result for HBV DNA as a serum level of HBV DNA < 100 IU/ml and defined macrovascular invasion as the presence of portal vein invasion (PVI) and/or hepatic vein invasion (HVI), which was detected by two different inspection methods, magnetic resonance imaging (MRI), or computed tomography (CT) accompanied by ultrasonographic testing. All imaging and ultrasonic reports were verified by at least two senior experts in related fields. We defined microscopic vascular invasion (MVI) as the invasion is visible only on microscopy and was assessed by several sections of non-tumoral hepatic parenchyma 1 cm away from the tumor according to previous studies [18, 19]. HBV reactivation was defined as a 10-fold or greater increase in HBV DNA level compared to the baseline level [20, 21].

### Follow-up and outcomes

All patients were followed up once a month in the first 3 months after hepatectomy and then every 3 months in subsequent months until 36 months after surgery or until death. Patients received routine blood tests, liver function tests, serum alpha-fetoprotein (AFP) assays, ultrasound and CT, or MRI at each reexamination. Recurrence-free survival (RFS) and overall survival (OS) were the outcomes of this study.

### Propensity score analysis

Because grouping was based only on perioperative AVT rather than randomization, propensity score matching (PSM) was used to reduce the imbalance between the two groups. All possible clinicopathological covariates, such as tumor number, tumor size, and vascular invasion, which might have affected the target outcomes were included when conducting the PSM. Propensity scores were evaluated using a logistic regression model in this study. Patients were matched at a 1:1 ratio using the caliper matching method within 0.2 of the standard deviation from the propensity score logit, basing on previous literatures [22–24]. And finally, we obtained the score-matched pairs for subsequent analyses.

### Statistics and analysis

Intergroup categorical data were analyzed with the $\chi^2$ test or Fisher's exact test, as appropriate. Univariate and multivariate analyses were performed using the Cox proportional hazards model. Survival curves were calculated and compared using the Kaplan-Meier method and log-rank test. All analyses were performed using SPSS version 22.0 (IBM, United States), and the PSM analysis was conducted in R (R Foundation for Statistical Computing, Austria). A two-tailed $P$ value of less than 0.05 was considered statistically significant.

## Results

### Clinicopathological characteristics

There were 728 such patients registered in our system. According to the inclusion and exclusion criteria, 161 HCC patients who tested positive for serum HBsAg but negative for HBV DNA before surgery were included. Among the selected 161 patients, 73 (45.34%) received AVT during the perioperative period and were included in the AVT group, while the remaining 88 (54.66%) were included in the non-AVT group (Fig. 1, Additional file 1). All patients were negative for hepatitis C virus (HCV) antibodies; did not receive adjuvant treatments, such as systemic chemotherapy, postoperative adjuvant TACE or transcatheter arterial embolization (TAE), and adoptive immunotherapy; had only HCC; and had the diagnosis of HCC pathologically confirmed after the surgery. During the postoperative follow-up period, patients who experienced HBV reactivation were administered entecavir and still be included in their initial groups.

Before the PSM analysis, most factors were balanced except Barcelona clinic liver cancer (BCLC) stage, tumor size, tumor capsule, vascular invasion, liver cirrhosis, anatomical hepatectomy, and HBV reactivation (all $p < 0.05$; Table 1). After PSM, all measured baseline variables were balanced between AVT group and non-AVT group, and finally, we generated 37 pairs of patients who had no significant differences in terms of all confounding factors for subsequent analysis (Table 1).

### HBV reactivation

Before PSM, there were two patients (2.74%) presented with HBV reactivation in the AVT group, while 20 patients (22.73%) presented with HBV reactivation in the non-AVT group, and this difference was statistically significant ($p < 0.01$). Patients who experienced reactivation were considered for subsequent antiviral therapy.

### Effect of antiviral therapy on recovery of liver function

At 1 day, 3 days, 5 days, and 7 days after hepatectomy, liver function parameters such as alanine aminotransferase, total bilirubin, albumin, and prothrombin time all showed no significant difference between AVT and non-AVT groups (Fig. 2a, b, d, all $p > 0.05$). However, albumin was significantly higher in the antiviral group than in the non-antiviral group at 1 month after hepatectomy, indicating better recovery of liver function to some extent (Fig. 2c, $p < 0.05$).

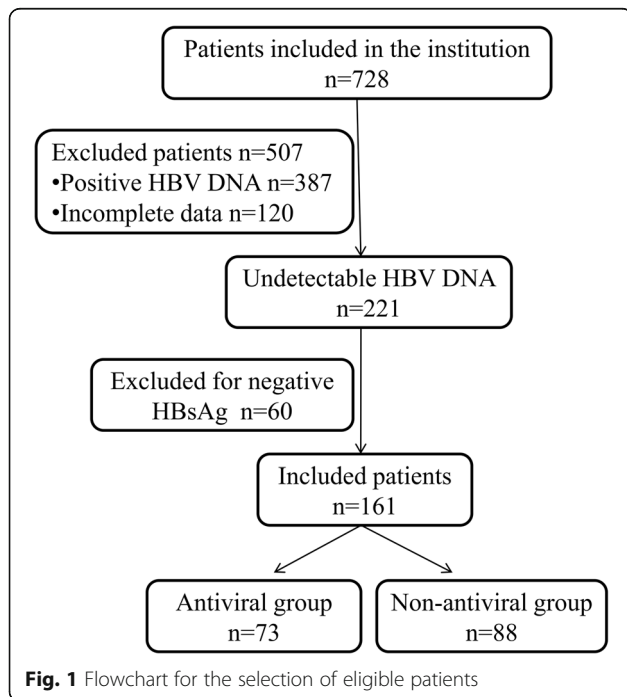### Independent risk factors of prognosis

The univariate and multivariate analyses are summarized in Table 2. On univariate analysis, BCLC stage, tumor size, tumor number, satellite nodule, blood loss, ALT, and HBV reactivation were identified as significant factors of RFS. Multivariate analysis revealed that tumor number (hazard ratio (HR) 5.39; 95% CI 2.276–12.766; $p < 0.01$) and HBV reactivation (HR 8.037; 95% CI 4.646–13.906; $p < 0.01$) were associated with RFS. Similarly, based on multivariate analysis, tumor size, anatomical hepatectomy, operative time, and HBV reactivation were related to overall survival (Table 3).

### Survival analysis before and after propensity matching analysis

Before propensity matching analysis, the 1-, 2-, and 3-year RFS rates were 80.82%, 69.86%, and 58.90% and 69.32%, 60.23%, and 55.68% in the AVT group and control group, respectively (Fig. 3a, $p = 0.279$); the 1-, 2-, and 3-year OS rates were 97.26%, 94.52%, and 93.15% and 90.91%, 86.36%, and 84.09% in the AVT group and non-AVT group, respectively (Fig. 3b, $p < 0.05$). After PSM, the 1-, 2-, and 3-year RFS rates in the AVT group and the non-AVT group were 78.38%, 72.97%, and 62.16% and 81.08%, 72.97%, and 72.97%, respectively (Fig. 4a, $p = 0.564$); however, the 1-, 2-, and 3-year OS rates were 97.30%, 97.3%, and 91.89% and 94.59%, 94.59%, and 86.49%, respectively, and there was no significant difference between the two groups (Fig. 4b, $p = 0.447$).
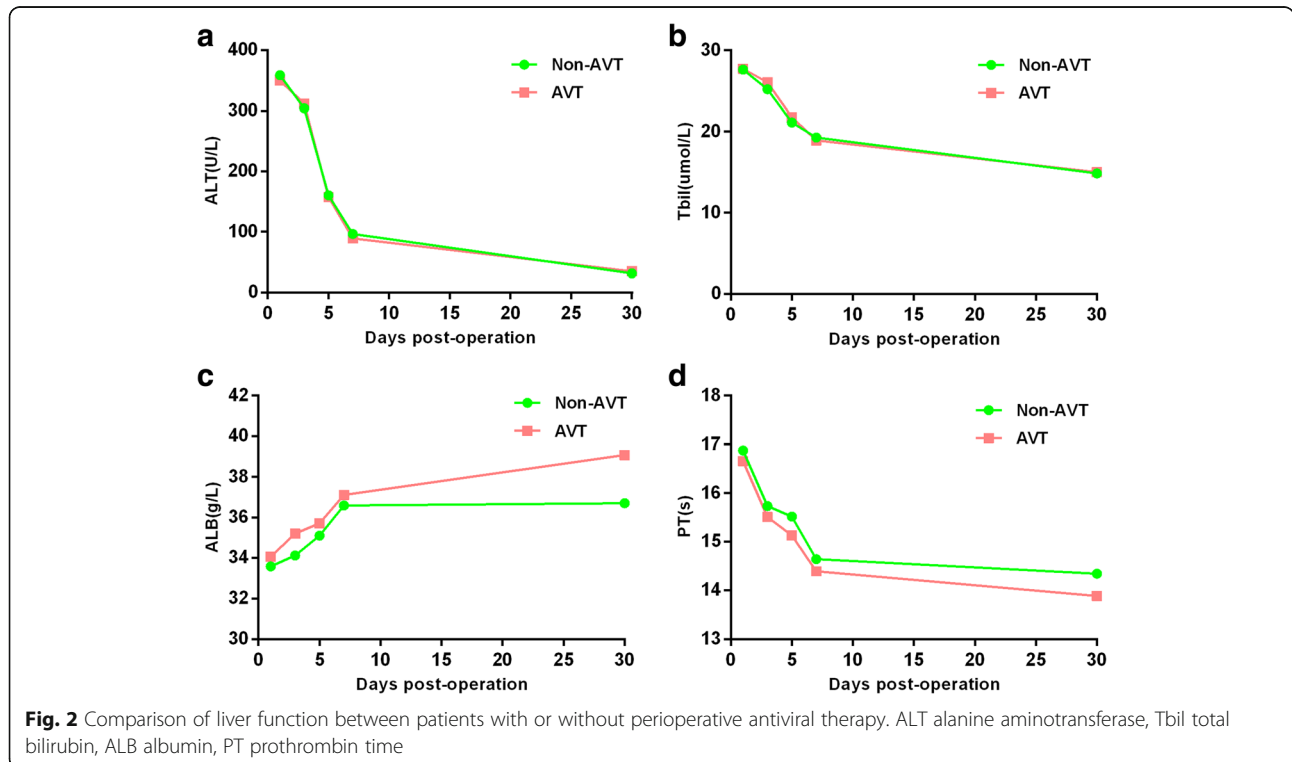
## Discussion

For patients who are positive for HBV DNA, official guidelines recommend antiviral therapy and rational drug selection [25–27]. Previous studies have indicated the necessity of antiviral treatment for HCC patients



**Fig. 1** Flowchart for the selection of eligible patients

Patients included in the institution
n=728

Excluded patients n=507
•Positive HBV DNA n=387
•Incomplete data n=120

Undetectable HBV DNA
n=221

Excluded for negative
HBsAg  n=60

Included patients
n=161

Antiviral group
n=73

Non-antiviral group
n=88

**Table 1** Clinicopathological variables between the two groups

| Variables | Before PSM | | | After PSM | | |
|---|---|---|---|---|---|---|
| | Non-antiviral n = 88 | Antiviral n = 73 | P value | Non-antiviral n = 37 | Antiviral n = 37 | P value |
| Gender, M/F | 76/12 | 66/7 | 0.428 | 31/6 | 32/5 | 0.744 |
| Age (year), < 50/≥ 50 | 39/49 | 43/30 | 0.065 | 19/18 | 20/17 | 0.816 |
| AFP level (ng/ml), < 400/≥ 400 | 58/30 | 48/25 | 0.751 | 22/15 | 22/15 | 1.000 |
| BCLC stage, 0,A/B,C | 49/39 | 55/18 | 0.009 | 28/9 | 24/13 | 0.309 |
| Tumor size (cm), < 5/≥ 5 | 40/48 | 52/21 | 0.001 | 26/11 | 25/12 | 0.802 |
| Tumor number, < 3/≥ 3 | 84/4 | 70/3 | 0.893 | 35/2 | 36/1 | 0.556 |
| Capsule integrity, yes/no | 54/34 | 62/11 | 0.001 | 27/10 | 26/11 | 0.797 |
| Satellite nodule, yes/no | 7/81 | 7/66 | 0.714 | 5/32 | 5/32 | 1.000 |
| Vascular invasion, yes/no | 36/52 | 17/56 | 0.018 | 8/29 | 12/25 | 0.295 |
| MVI, yes/no | 3/85 | 5/68 | 0.317 | 1/36 | 2/35 | 0.556 |
| Necrosis, yes/no | 18/70 | 9/64 | 0.169 | 4/33 | 4/33 | 1.000 |
| Liver cirrhosis, yes/no | 41/47 | 52/21 | 0.002 | 19/18 | 22/15 | 0.483 |
| PHT, yes/no | 32/56 | 31/42 | 0.430 | 13/24 | 15/22 | 0.632 |
| Anatomical hepatectomy, yes/no | 32/56 | 39/34 | 0.030 | 14/23 | 15/22 | 0.812 |
| Blood loss (ml), < 500/≥ 500 | 75/13 | 62/11 | 0.958 | 31/6 | 33/4 | 0.496 |
| Operative time (min), < 120/≥ 120 | 3/85 | 7/66 | 0.106 | 1/36 | 0/37 | 0.314 |
| ALT (U/L), < 40/≥ 40 | 51/37 | 44/29 | 0.766 | 22/15 | 23/14 | 0.812 |
| ALB (g/L), ≤36/> 36 | 16/72 | 10/63 | 0.442 | 7/30 | 6/31 | 0.760 |
| PT (s), < 13/≥ 13 | 63/25 | 52/21 | 0.960 | 27/10 | 27/10 | 1.000 |
| HBV reactivation, yes/no | 20/68 | 2/71 | 0.001 | 3/34 | 2/35 | 0.643 |

PSM propensity score matching, AFP alpha-fetoprotein, BCLC Barcelona clinic liver cancer, MVI microvascular invasion, PHT portal hypertension, ALT alanine aminotransferase, ALB albumin, PT prothrombin time, HBV hepatitis B virus



**Fig. 2** Comparison of liver function between patients with or without perioperative antiviral therapy. ALT alanine aminotransferase, Tbil total bilirubin, ALB albumin, PT prothrombin time

**Table 2** Prognostic factors associated with recurrence-free survival

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | p value | HR | 95% CI | p value | HR | 95% CI |
| Gender | 0.259 | | | | | |
| Age | 0.895 | | | | | |
| AFP | 0.381 | | | | | |
| BCLC | 0.044 | 1.656 | 1.013–2.707 | | | |
| Tumor size | 0.040 | 1.663 | 1.022–2.706 | | | |
| Tumor number | 0.001 | 4.288 | 1.843–9.978 | < 0.01 | 5.390 | 2.276–12.766 |
| Capsule integrity | 0.650 | | | | | |
| Satellite nodule | 0.018 | 2.352 | 1.161–4.763 | | | |
| Vascular invasion | 0.215 | | | | | |
| MVI | 0.582 | | | | | |
| Necrosis | 0.199 | | | | | |
| Liver cirrhosis | 0.077 | | | | | |
| PHT | 0.636 | | | | | |
| Anatomical hepatectomy | 0.137 | | | | | |
| Blood loss | 0.028 | 1.946 | 1.076–3.517 | | | |
| Operative time | 0.509 | | | | | |
| ALT | 0.042 | 1.655 | 1.017–2.693 | | | |
| ALB | 0.726 | | | | | |
| TB | 0.130 | | | | | |
| PT | 0.757 | | | | | |
| Antiviral therapy | 0.280 | | | | | |
| HBV reactivation | < 0.01 | 7.490 | 4.359–12.870 | < 0.01 | 8.037 | 4.646–13.906 |

*AFP* alpha-fetoprotein, *BCLC* Barcelona clinic liver cancer, *MVI* microvascular invasion, *PHT* portal hypertension, *ALT* alanine aminotransferase, *ALB* albumin, *TB* total bilirubin, *PT* prothrombin time, *HBV* hepatitis B virus

with chronic HBV infection; however, it remains controversial whether it is also necessary to implement antiviral treatment for patients with undetectable levels of HBV DNA [28, 29]. Similarly, HCC patients who are negative for HBV DNA also encounter the uncertainty.

The high recurrence rate and the development of postoperative metastasis are always important issues for clinicians and patients. It has been reported that the HCC recurrence rate within 5 years after hepatectomy is as high as 70% [30–32]. Tumor size, tumor number, tumor stage, tumor differentiation, MVI, etc. are all factors that influence postoperative recurrence in HCC patients [33, 34], and this is also consistent with results of our

univariate and multivariate analyses (Table 2). At the same time, it is clear that a positive HBV DNA test is an independent risk factor for postoperative recurrence. Numerous studies have shown that a high serum level of HBV DNA (more than 2000 IU/ml) is an independent risk factor for the development of HCC in chronic hepatitis B patients, and higher serum levels of HBV DNA are more likely to be associated with the occurrence of liver cancer than lower levels of HBV DNA [35–37]. It has also been confirmed that surgery may cause HBV reactivation with a high viral load, thus increasing the risk of tumor recurrence; therefore, AVT is required for those patients [15, 38]. However, studies about patients with very low viral load levels, such as the HBV DNA level < 100 IU/ml used in this study, are almost nonexistent, and currently, there are no guidelines for those patients.

To the best of our knowledge, this is the first study exploring the effects of AVT on prognoses in HCC patients who are positive for serum HBsAg but negative for HBV DNA (HBV DNA < 100 IU/ml).

Our results showed that antiviral therapy can substantially reduce the postoperative HBV reactivation rate, which was consistent with the results of previous studies [39–41]. In terms of HBV reactivation, there is no exact mechanism that has been proposed to explain the mechanism by which HBV reactivation occurs after surgery. Some scholars believe that the surgery itself leads to this outcome because hepatectomy may induce immune-suppression [42–44]. Other studies suggest that the presence of covalently closed circular DNA in hepatocyte nuclei may be the reason for later reactivation [45–47]. Taken together, the administration of perioperative AVT for a prolonged period of time, such as the 1 year used in this study, perhaps would be helpful to reduce HBV reactivation.
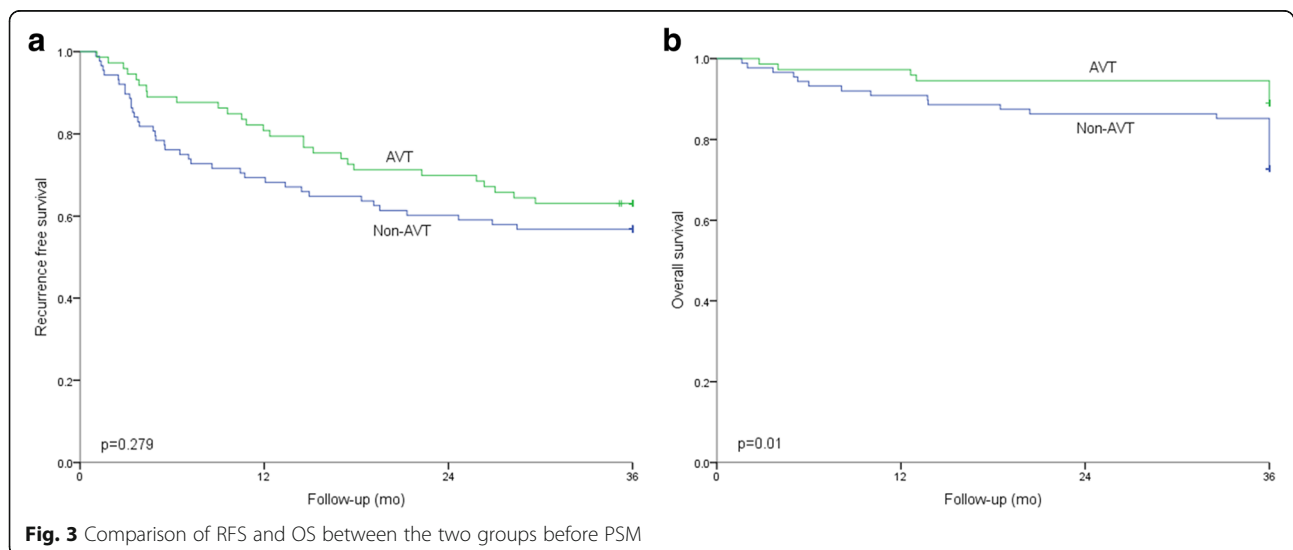
Our results indicate that perioperative antiviral therapy does not improve liver function in 1 week after hepatectomy, but can better promote albumin recovery than non-antiviral therapy at 1 month, which is consistent with previous studies [15, 48]. The reason for the results, we suppose, is the temporality of antiviral therapy, that is, when early stage after operation, the hepatectomy itself dominates the recovery of liver function; however, with the regeneration of residual liver, the influence of surgical factor gradually weakens and the influence of antiviral therapy gradually strengthens.
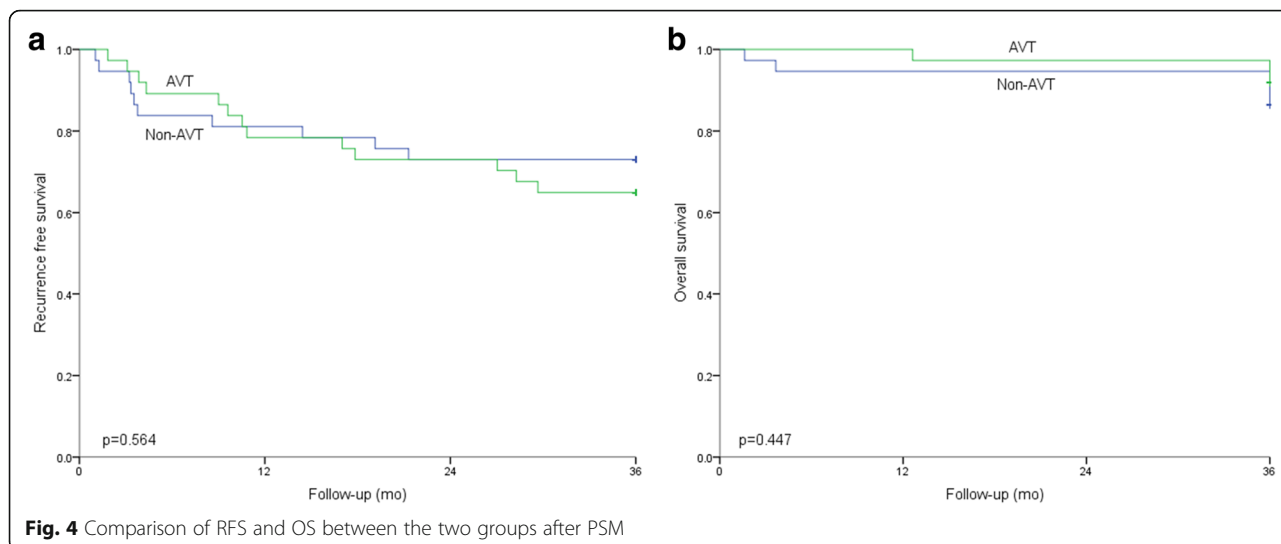
In this study, we concluded that antiviral therapy may not improve RFS. On the other hand, although there was no significant difference in OS rates between the two groups, we still observed that OS in the antiviral group was higher than that in the non-antiviral group; we hypothesized that the lack of a significant difference may be the result of the small sample size, and studies with larger samples sizes are needed in the future. The

**Table 3** Prognostic factors associated with overall survival

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | *p* value | HR | 95% CI | *p* value | HR | 95% CI |
| Gender | 0.680 | | | | | |
| Age | 0.925 | | | | | |
| AFP | 0.403 | | | | | |
| BCLC | 0.018 | 2.320 | 1.158–4.645 | | | |
| Tumor size | 0.001 | 3.875 | 1.793–8.376 | < 0.01 | 5.092 | 2.174–11.926 |
| Tumor number | 0.066 | | | | | |
| Capsule integrity | 0.920 | | | | | |
| Satellite nodule | 0.811 | | | | | |
| Vascular invasion | 0.017 | 2.319 | 1.160–4.639 | | | |
| MVI | 0.634 | | | | | |
| Necrosis | 0.351 | | | | | |
| Liver cirrhosis | 0.820 | | | | | |
| PHT | 0.365 | | | | | |
| Anatomical hepatectomy | 0.044 | 0.484 | 0.239–0.981 | 0.034 | 0.463 | 0.227–0.944 |
| Blood loss | 0.051 | | | | | |
| Operative time | 0.009 | 3.590 | 1.379–9.345 | < 0.01 | 7.064 | 2.433–20.512 |
| ALT | 0.986 | | | | | |
| ALB | 0.654 | | | | | |
| TB | 0.214 | | | | | |
| PT | 0.629 | | | | | |
| Antiviral therapy | 0.016 | 0.375 | 0.168–0.834 | | | |
| HBV reactivation | < 0.01 | 5.353 | 2.641–10.848 | < 0.01 | 5.190 | 2.545–10.582 |

*AFP* alpha-fetoprotein, *BCLC* Barcelona clinic liver cancer, *MVI* microvascular invasion, *PHT* portal hypertension, *ALT* alanine aminotransferase, *ALB* albumin, *TB* total bilirubin, *PT* prothrombin time, *HBV* hepatitis B virus



**Fig. 3** Comparison of RFS and OS between the two groups before PSM

**Fig. 4** Comparison of RFS and OS between the two groups after PSM

conclusion of OS rates was different from that of a previous study [49], and the main reason for this difference may have been the different HBV DNA levels between the two studies. To define a patient as having a negative result for HBV DNA, we had a more stringent standard (HBV DNA < 100 IU/ml), which was much lower than the standard used in the other study (HBV DNA < $1.0 \times 10^3$ IU/ml). Perhaps, with such an extremely low viral load, HBV was in a very stable state and seldom caused inflammation of the liver or an immune response; thus, AVT was not able to exert any influence on tumor recurrence and patient survival. Of course, this conjecture requires more supporting research.

This study had some limitations. First, it was a single-center study. Second, the research period was large, and the importance of AVT for HCC patients has gradually changed over the years, leading to the large initial baseline heterogeneity of patients administered AVT. Third, given that this study was a retrospective study, the duration of AVT was inconsistent. In addition, the sample size may have been a limiting factor for the separation of the KM curves when analyzing OS, and the role played by the tumor-immune microenvironment during this process is still unknown. At the same time, patients' data about HBeAg, anti-HBe, and HBV phase was absent restricted by the detection means.

## Conclusions

In conclusion, AVT can reduce the HBV reactivation rate but has no effect on survival for HCC patients who are negative for HBV DNA (HBV DNA < 100 IU/ml). This conclusion will be useful for selecting treatment methods for this type of patient. However, studies with larger sample size are needed to further verify this conclusion and explore the possible mechanism underlying this result.

## Additional files

**Additional file 1:** Eligible patients included in the AVT and non-AVT group. (XLSX 68 kb)

**Abbreviations**
AFP: Alpha-fetoprotein; ALB: Albumin; ALT: Alanine aminotransferase; AVT: Antiviral therapy; BCLC: Barcelona clinic liver cancer; CT: Computed tomography; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; HVI: Hepatic vein invasion; MRI: Magnetic resonance imaging; MVI: Microvascular invasion; OS: Overall survival; PHT: Portal hypertension; PSM: Propensity score matching; PT: Prothrombin time; PVI: Portal vein invasion; RFS: Recurrence-free survival; TACE: Transcatheter arterial chemoembolization; TAE: Transcatheter arterial embolization; TB: Total bilirubin; VR: Virological response

**Availability of data and materials**
The authors presented all necessary information about the study in the manuscript and its supplementary material.

**Authors' contributions**
YSZ and NL designed the study. MXX, ZZ, and HLZ collected the data. RYX and NL performed the statistical analysis. MXX and ZZ drafted the manuscript. RYX and YSZ revised and proofread the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**
All patients in this study provided informed consent before undergoing hepatectomy. All procedures in this study were performed in accordance with the principles of the Research Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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## Author details

[1]Department of Hepatobiliary Surgery, The Third Affiliated Hospital of Sun Yat-Sen University, No. 600 Tianhe Road, Guangzhou 510630, Guangdong, China. [2]Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital and Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China.

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