






Antiviral Treatments Eliminate the Adverse Impacts of High Baseline HBV Loads on the Survival of HBV-Related HCC Patients

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Background: In consideration of no standard exclusion criteria for hepatitis B virus (HBV) loads in hepatocellular carcinoma (HCC)-related clinical trials, this study aimed to investigate the prevalence of HBV-related exclusion criteria among current clinical trials and evaluate whether antiviral treatments could eliminate the adverse effects from high HBV loads for HCC patients.

Methods: This is a retrospective study including 772 HCC clinical trials on ClinicalTrials.gov and 1784 HCC patients receiving antiviral treatment. The Kaplan–Meier (K-M) method was used to compare the progression-free survival (PFS) and overall survival (OS) between different groups, and Cox regression analyses were performed to validate possible risk factors on PFS and overall survival OS.

Results: Among 772 clinical trials, 58.3% did not adopt baseline HBV loads as exclusion criteria, 18.0% was 2000 IU/mL, and 10.5% was receiving antiviral therapy. We observed baseline HBV loads had no significant impact on PFS ($p = 0.491, 0.155, 0.119, 0.788, 0.280, 0.683$ respectively) and OS ($p = 0.478, 0.741, 0.263, 0.039, 0.999, 0.581$ respectively) in all patients or each treatment group including hepatectomy, radiofrequency ablation, interventional therapy, targeted drugs and anti-programmed cell death immunotherapy, except for the OS of interventional therapy group, where patients with high HBV loads had higher BCLC stage, serum AFP level and ALBI grade ($p = 0.009, 0.015$ and 0.003 , respectively).

Conclusion: Antiviral treatments could eliminate the adverse impacts of high HBV loads on the survival of HCC patients. Simplified eligibility criteria can be adopted for HCC patients with HBV infection where regular antiviral therapy should be enough.

Keywords: hepatocellular carcinoma, hepatitis B virus loads, antiviral treatment, exclusion criteria, clinical trials

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancy and ranks as the third leading cause of cancer-related mortality.¹ Although curative treatments achieve promising survival in patients with early-stage HCC, the prognosis remains dismal among those at advanced stage.² Clinical trials can help solve this dilemma by identifying effective therapies for patients with advanced HCC such as lenvatinib by the REFLECT trial and atezolizumab plus bevacizumab by the IMbrave150 trial.^{3,4} However, clinical trials are currently in crisis due to low patient accrual rates, which impede the completion of trials.^{5,6} Obstacles to patient enrollment can extend trial duration and limit the generalizability of trials, and complex eligibility criteria are a major barrier to patient accrual.^{7,8}

Approximately 54% HCC patients are infected with hepatitis B virus (HBV), the proportion of which reaches to 70–80% in endemic region.⁹ However, clinical trials usually exclude HCC patients with high baseline HBV loads. For instance, HCC patients with HBV loads >100IU/mL were excluded from CheckMate 040, and they were consistently omitted from KEYNOTE-224.^{10,11} Eligibility criteria from previous protocols are reflexively applied to clinical trials with similar study populations without scientific justification.¹² The reflexive exclusion of HCC patients with HBV infection from trials is presumably for the concerns that high baseline HBV loads can adversely affect or interfere with clinical outcomes.¹³ All HBsAg-positive HCC patients are recommended to accept NAs therapy.^{14,15} With effective antiviral drugs such as entecavir and tenofovir, however, few studies have explored whether antiviral treatments could reverse the adverse impact of high baseline HBV loads on clinical outcomes, which can potentially expand the enrollment of clinical trials.

This study aimed to investigate the prevalence of HBV-related exclusion criteria among current clinical trials and to evaluate whether antiviral treatments could eliminate the adverse effects from high HBV loads for HCC patients, which assisted to identify reasonable inclusion criteria for HCC patients and improve the accrual rates of clinical trials.

Materials and Methods

Clinical Trials Selection

To investigate the prevalence of requirements of baseline HBV loads among HCC clinical trials, we reviewed HCC clinical trials on ClinicalTrials.gov. Trials with “withdrawn status” were excluded considering that their protocols might be unreasonable. We also excluded trials lacking necessary information or enrolling other tumors except for HCC. Finally, 772 HCC clinical trials were included for analysis. Detailed description of trials enrollment is shown in [Figure 1](#).

Patient Selection

We retrospectively reviewed the clinical data on consecutive HCC patients in Sun Yat-sen University Cancer Center from January 2011 to December 2020. The inclusion criteria of patients were as following: 1) age at diagnosis ≥ 18 years old; 2) clinically or pathologically diagnosed as HCC according to ESMO guidelines and 3) with positive hepatitis B virus surface antigen (HBsAg). Patients were excluded when meeting any of the following criteria: 1) without pretreatment baseline HBV DNA tests; 2) coinfecting with other hepatitis viruses such as hepatitis C virus; 3) only receiving best supportive care; 4) incomplete clinical data; 5) initiating antiviral treatments more than one week after initial anti-HCC therapy or 6) receiving other antiviral drugs except for entecavir or tenofovir. Eventually, a total of 1784 HCC patients were included for analysis in this study. The treatment modalities can be classified into hepatectomy, radiofrequency ablation (RFA), interventional therapy, targeted drugs and anti-programmed cell death (PD)

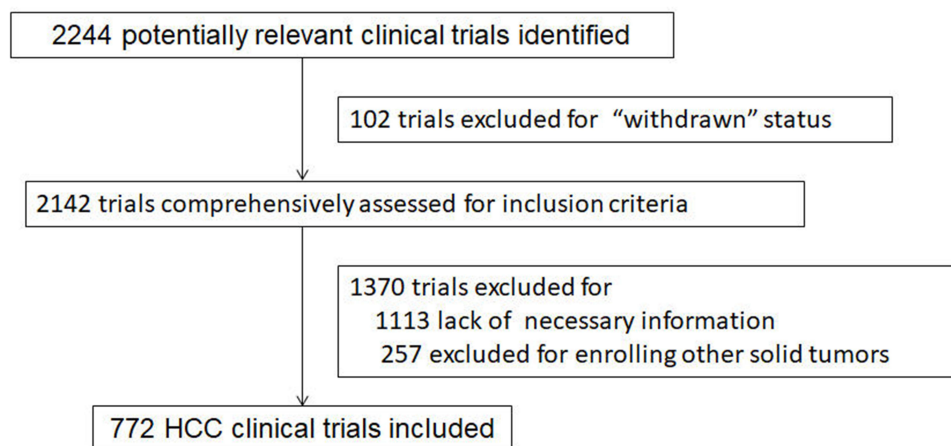


Figure 1 Flow diagram of HCC clinical trials enrollment on ClinicalTrials.gov.

immunotherapy. Serum HBV loads was measured by real-time viral polymerase chain reaction with a lower detection limit of 30 IU/mL.

Statistical Analysis

The demographic and clinical characteristics were compared between HCC patients with baseline HBV loads <2000 IU/mL and those with baseline HBV loads \geq 2000 IU/mL. Two-sample independent *t*-test was adopted to compare age at diagnosis with a normal distribution. Chi-square test was performed to compare categorical characteristics between the two groups. The Kaplan–Meier (K-M) method was used to compare the progression-free survival (PFS) and overall survival (OS) between groups with high and low baseline HBV loads. The PFS was defined as the period from initial treatments to the first progression or death. The OS was measured from the time of initial treatments to the date of death or last follow-up. Cox regression model was adopted to identify significant factors for the PFS and OS including age at diagnosis, gender, Barcelona Clinic Liver Cancer (BCLC) stage, serum alpha-fetoprotein (AFP) level, albumin-bilirubin (ALBI) grade, treatment modalities and antiviral drugs. The analyses were performed using IBM SPSS, version 25.0. The survival curves were plotted with R software version 3.3.2. A two-tailed *P* value <0.05 was statistically significant.

Results

Characteristics of Included Trials and HBV Exclusion Criteria

They included 772 clinical trials enrolling a total of 98,340 patients. The characteristics and relevant HBV loads exclusion criteria are summarized in [Table 1](#). Among these trials, 58.3% (450/772) did not adopt baseline HBV loads as exclusion criteria. The criteria of HBV infection varied among protocols of the rest trials. The most common cutoff value of exclusion criteria for HBV loads was 2000 IU/mL (18.0%, 139/772). Receiving antiviral therapy was the secondary most common inclusion criteria for patients with HBV-related HCC (10.5%, 81/772). The other common cutoff values of HBV loads for exclusion criteria were 100 IU/mL, 500 IU/mL and 0 IU/mL. The association between clinical trial characteristics and HBV-related exclusion criteria is shown in [Supplementary Table 1](#). Overall, HBV-related exclusion criteria were more common in Phase I/II trials and trials for systemic treatments. Besides, modern trials excluded HCC patients with high HBV loads more often. The proportion of exclusion criteria for HBV loads increased with the stage of HCC.

Patient Characteristics

The clinical characteristics of 1784 HCC patients are presented in [Table 2](#). No significant association was found between baseline HBV loads and age or gender. Patients with baseline HBV loads \geq 2000 IU/mL had more advanced HCC than those with baseline HBV loads <2000 IU/mL. Serum AFP level had a similar trend. The liver function was slightly worse in the group with high HBV loads. The use of type of antiviral drugs was similar between groups with high and low baseline HBV loads. To specifically evaluate the impact of HBV loads on survival, patients were further classified into subgroups according to their initial treatment modalities. Among the whole cohort, 870 patients received hepatectomy, 109 patients received RFA, 424 patients were treated with interventional therapy including transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC), 187 patients were treated with targeted drugs and 194 patients received anti-PD-1 immunotherapy.

Impact of Baseline HBV Loads on the Survival of HCC Patients

The median follow-up time was 43.03 months. During the follow-up, 53.5% (955/1784) suffered from disease progression, and 27.2% (487/1784) of patients died. No significant difference was found in PFS between patients with baseline HBV loads <2000 IU/mL and those with baseline HBV loads \geq 2000 IU/mL (*p* = 0.491). The survival curves are shown in [Figure 2A](#). Similar trends were detected when the cutoff values were set at 500 IU/mL, 100 IU/mL and 0 IU/mL (*p* = 0.296, 0.463 and 0.521 respectively). In multivariate analysis, BCLC stage, serum AFP level, ALBI grade and treatment

Table I Characteristics of HCC Clinical Trials and Their HBV Loads Related Exclusion Criteria

Characteristics	Number of Trials (%)
Total	772
Stage of HCC	
Early	53 (6.9)
Early & Locoregionally advanced	97 (12.6)
Locoregionally advanced	145 (18.8)
Locoregionally advanced and Advanced	187 (24.2)
Advanced	290 (37.6)
Treatment modalities	
Curative treatments	41 (5.3)
Interventional treatments	171 (22.2)
Radiotherapy	48 (6.2)
Systemic treatments	512 (66.3)
Phase of study	
I	133 (17.2)
II	433 (56.1)
III	168 (21.8)
IV	38 (4.9)
Sample size	
Median (range)	50 (1–1714)
< 50	375 (48.6)
50–100	148 (19.2)
> 100	249 (32.3)
Involved type of endpoints	
Survival	696 (90.2)
Response	484 (62.7)
Adverse events/toxicity	440 (57.0)
Years of study activation	
1996–2005	47 (6.1)
2006–2015	370 (47.9)
2016–2021	355 (46.0)
Cutoff values of exclusion criterion for HBV loads	
0–100 IU/mL	50 (6.5)

(Continued)

Table 1 (Continued).

Characteristics	Number of Trials (%)
100–2000 IU/mL	176 (22.8)
> 2000 IU/mL	7 (0.9)
Coinfection with hepatitis C virus	8 (1.0)
Receiving antiviral therapy	81 (10.5)
None	450 (58.3)

Table 2 Baseline Demographic and Clinical Characteristics of HCC Patients with Different Baseline HBV Loads

Characteristics	HBV Loads < 2000 IU/mL	HBV Loads ≥ 2000 IU/mL	P value
Sample size	924	860	
Age, years	51.2±12.0	51.4±12.3	0.717
Gender			0.709
Male	807 (87.3%)	746 (86.7%)	
Female	117 (12.7%)	113 (13.3%)	
BCLC stage			< 0.001
0	124 (13.4%)	44 (5.1%)	
A	382 (41.3%)	385 (44.8%)	
B	234 (25.3%)	249 (29.0%)	
C	184 (19.9%)	182 (21.2%)	
AFP level, ng/mL			0.004
< 400	612 (66.2%)	513 (59.7%)	
≥ 400	312 (33.8%)	347 (40.3%)	
ALBI grade			< 0.001
I	708 (76.6%)	570 (66.3%)	
II	216 (23.4%)	290 (33.7%)	
Treatment modality			<0.001
Hepatectomy	435 (47.1%)	435 (50.6%)	
RFA	85 (9.2%)	24 (2.8%)	
Interventional therapy	192 (20.8%)	232 (27.0%)	
Targeted drugs	112 (12.1%)	75 (8.7%)	
Anti-PD-I immunotherapy	100 (10.8%)	94 (10.9%)	
Antiviral drugs			0.436
Tenofovir	267 (28.9%)	263 (30.6%)	
Entecavir	657 (71.1%)	597 (69.4%)	

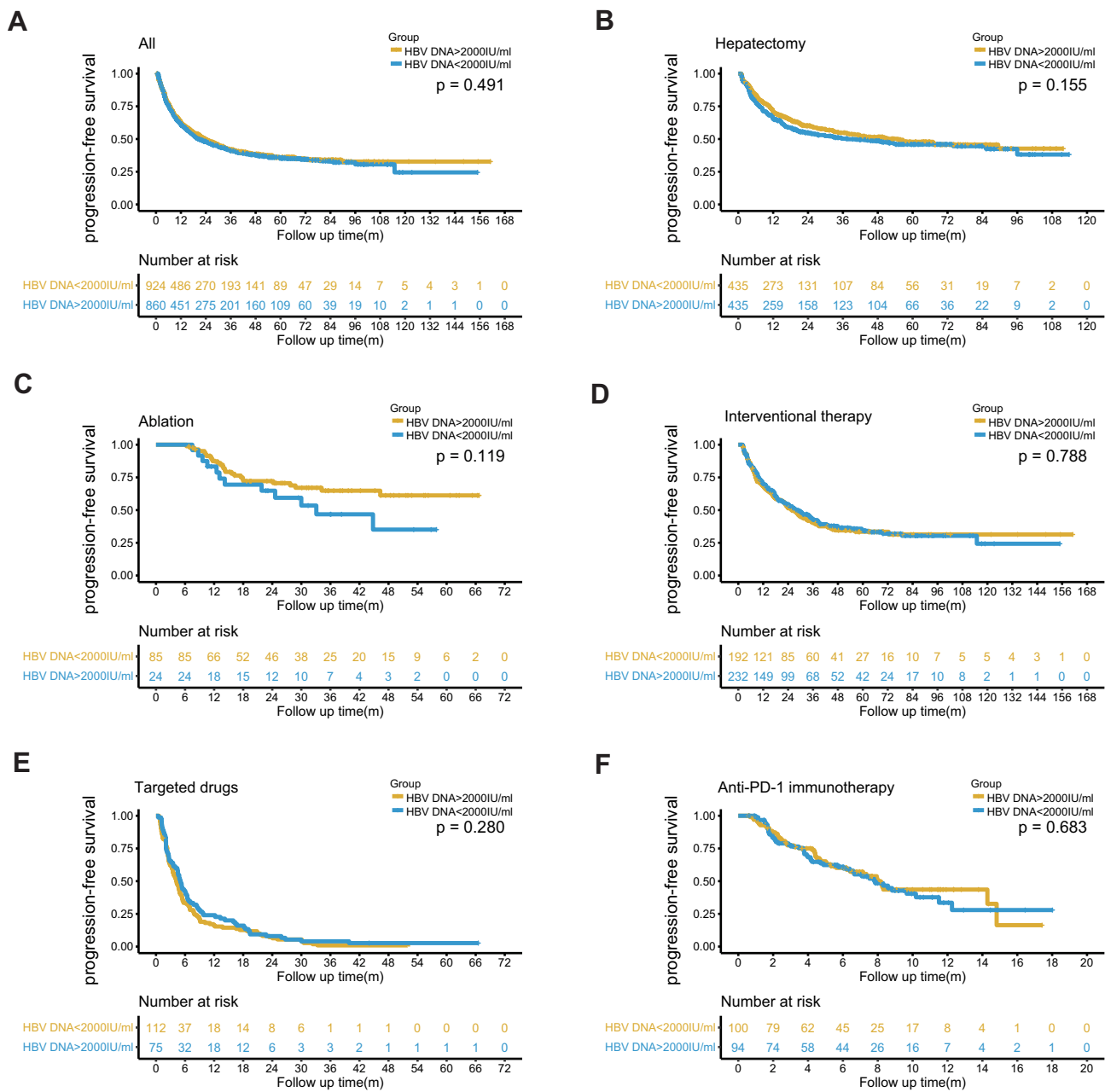


Figure 2 Kaplan–Meier curves of progression-free survival in all HCC patients (A) or different treatment group (B–F).

modalities were significantly associated with PFS. Detailed data are listed in Table 3. Baseline HBV loads had no significant impact on PFS ($p = 0.491$; hazard ratio (HR), 1.05; 95% confidence interval (CI), 0.92–1.19).

The OS was also similar between HCC patients with HBV loads <2000 IU/mL and those with HBV loads ≥ 2000 IU/mL ($p = 0.478$) (Figure 3A). Similarly, the OS did not differ significantly between groups with low and high baseline HBV loads when the cutoff values were set at 500 IU/mL, 100 IU/mL and 0 IU/mL ($p = 0.539$, 0.842 and 0.898 respectively). In univariate analysis, BCLC stage was significantly correlated with OS ($p < 0.001$). Serum AFP had negative association with OS ($p < 0.001$). Similarly, patients with higher ALBI grade had worse survival ($p < 0.001$). Treatment modalities were also associated with OS significantly ($p < 0.001$). Patients receiving tenofovir had longer OS than those receiving entecavir ($p < 0.001$). The above factors remained significant in the multivariate analysis (Table 3). However, no significant association was detected between baseline HBV loads and OS ($p = 0.478$; HR, 1.07; 95% CI, 0.89–1.27).

Table 3 Univariate and Multivariate Analyses for Prognostic Factors of PFS and OS

Variables	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age, years		0.075				0.209		
<60	I				I			
≥60	0.88 (0.76–1.01)				0.88 (0.72–1.07)			
Gender		0.132				0.343		
Female	I				I			
Male	1.16 (0.96–1.41)				1.14 (0.87–1.50)			
BCLC stage		<0.001		<0.001		<0.001		<0.001
0	I		I		I		I	
A	1.50 (1.13–2.00)	0.005	1.52 (0.93–2.47)	0.096	4.25 (1.99–9.09)	<0.001	1.80 (0.66–4.89)	0.250
B	2.46 (1.84–3.27)	<0.001	2.39 (1.43–4.00)	0.001	7.25 (3.40–15.50)	<0.001	2.52 (0.90–7.07)	0.079
C	4.98 (3.72–6.67)	<0.001	2.46 (1.42–4.28)	0.001	26.35 (12.39–56.07)	<0.001	4.08 (1.41–11.76)	0.009
AFP level, ng/mL		<0.001		<0.001		<0.001		<0.001
< 400	I		I		I		I	
≥ 400	1.56 (1.38–1.78)		1.38 (1.21–1.57)		2.17 (1.81–2.59)		1.78 (1.48–2.13)	
ALBI grade		<0.001		0.034		<0.001		<0.001
I	I		I		I		I	
II	1.53 (1.34–1.76)		1.17 (1.01–1.35)		2.39 (2.00–2.86)		1.61 (1.33–1.94)	
Treatment modality		<0.001		<0.001		<0.001		<0.001
Hepatectomy	I		I		I		I	
RFA	0.65 (0.47–0.91)	0.011	1.07 (0.61–1.90)	0.811	0.16 (0.05–0.49)	0.001	0.30 (0.07–1.36)	0.119
Interventional therapy	1.21 (1.03–1.42)	0.019	0.82 (0.66–1.01)	0.061	1.57 (1.24–1.98)	<0.001	0.92 (0.66–1.28)	0.630
Targeted drugs	5.17 (4.32–6.18)	<0.001	3.12 (2.33–4.17)	<0.001	8.87 (7.03–11.19)	<0.001	3.73 (2.49–5.59)	<0.001
Anti-PD-1 immunotherapy	2.97 (2.35–3.74)	<0.001	1.75 (1.28–2.40)	<0.001	6.19 (4.35–8.82)	<0.001	2.50 (1.55–4.04)	<0.001
HBV loads, IU/mL		0.491				0.478		
<2000	I				I			
≥2000	1.05 (0.92–1.19)				1.07 (0.89–1.27)			
Antiviral drugs		0.769				<0.001		0.045
Tenofovir	I				I		I	
Entecavir	1.02 (0.89–1.18)				1.50 (1.20–1.87)		1.26 (1.01–1.59)	

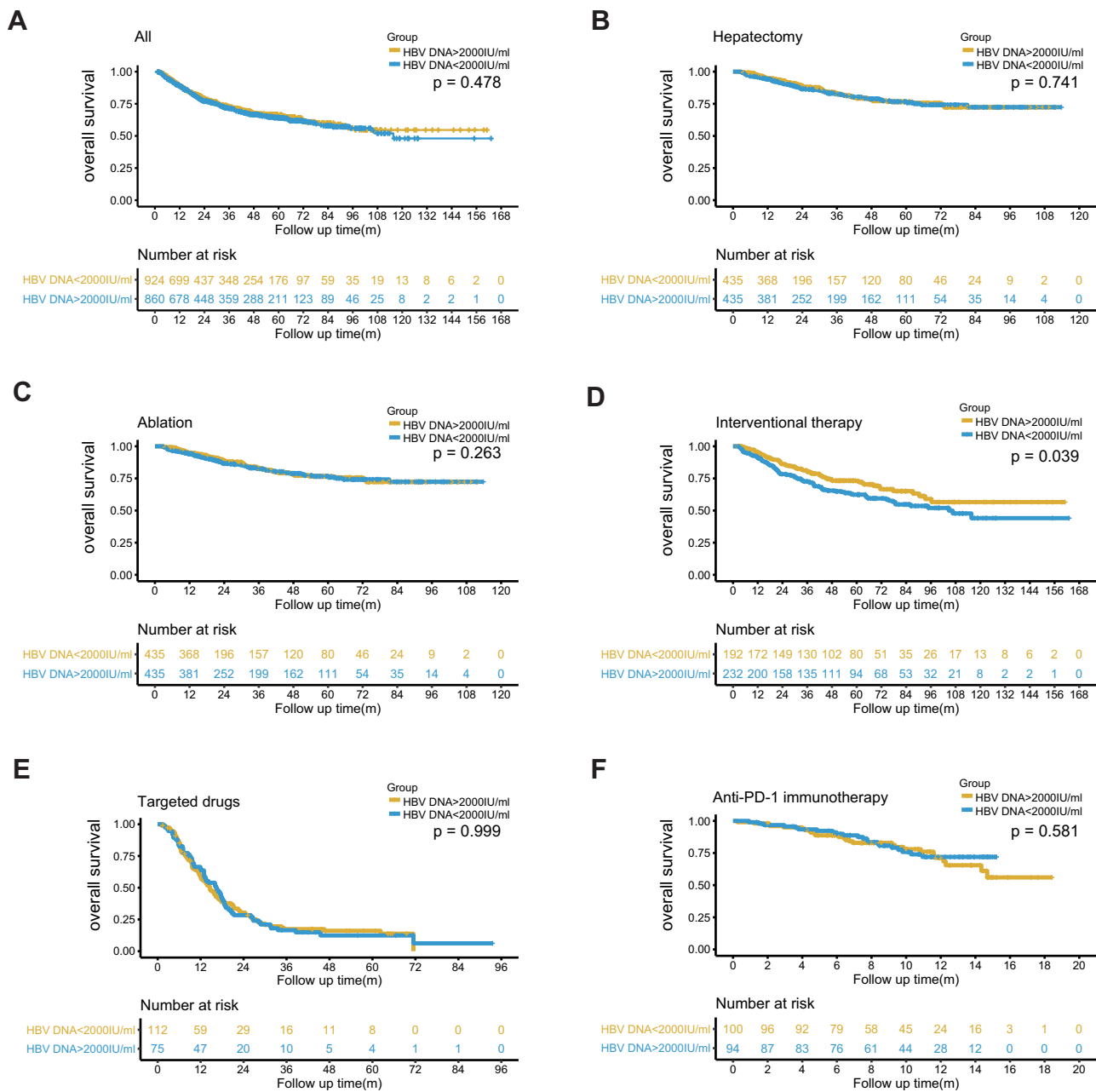


Figure 3 Kaplan–Meier curves of overall survival in all HCC patients (A) or different treatment group (B–F).

Impact of Baseline HBV Loads Classified by Treatment Modality

To specifically evaluate the prognostic impact of HBV in each treatment modality, we further compared the survival between patients with low and high baseline HBV loads in each subgroup classified by treatments. There was no significant association between PFS and baseline HBV loads in each treatment group. The survival curves are shown in Figure 2B–F. In terms of OS, patients with high baseline HBV loads had similar survival compared to those with low HBV loads in all subgroups except for the group receiving interventional therapy (Figure 3B–F). In group with intervention treatment, patients with high HBV loads had higher BCLC stage, serum AFP level and ALBI grade ($p = 0.009, 0.015$ and 0.003 , respectively). After multivariate analyses, baseline HBV loads did not correlate with OS significantly in HCC patients receiving interventional therapy ($p = 0.317$; HR, 1.20; 95% CI, 0.84–1.70).

Discussion/Conclusion

In this study, we reviewed clinical trials for HCC and found that 41.7% trials adopted baseline HBV loads as exclusion criteria. To validate the validity of this criterion, we compared the prognosis of HCC patients who received antiviral treatments but had different baseline HBV loads and found that antiviral treatments could eliminate the adverse impact of high HBV loads on the survival of HCC patients. These findings could assist in increasing patient enrollment and improving the efficiency and generalizability of clinical trials.

In recent years, the first-line treatments of HCC have been updated by the results from clinical trials such as lenvatinib from the REFLECT trial and atezolizumab plus bevacizumab from the IMbrave150 trial.^{3,4} Anti-PD-1 immunotherapy has changed the landscape of treatments for unresectable HCC, and oncologists are exploring how to improve the survival of HCC patients by the combination of immunotherapy and other treatment modalities, which are mainly based on clinical trials.¹⁶ Clinical trials improve the management of patients and prove the feasibility of new treatments. However, only 2–4% cancer patients are recruited in trials, and half of National Cancer Institute-sponsored trials are completed.^{17,18} Low accrual rates can prolong the duration of enrollment, which increases the risk of termination of trials.¹⁸ Barriers to enrollment involve clinician, patient and trial factors, among which strict eligibility criteria is a major obstacle. Strict inclusion criteria may compromise the generalizability of clinical trials and prevent potential beneficiaries from accessing new therapies.¹⁹ Despite proposals for simplified and rational criteria, eligibility criteria have become more complex and stringent over time. Our results showed that the proportion of HBV-related exclusion criteria had been increasing over years. Excluding HCC patients with high baseline HBV loads may be due to the long-held belief that high HBV loads can cause adverse impacts on the survival. However, few studies have evaluated the rationality of this criterion. Considering the high prevalence of HBV in HCC patients, this eligibility criterion can severely limit accrual rates.

Currently, the criteria of HBV infection varied among clinical trials. Different cutoff values were set for exclusion criteria, while some trials only required patients to receive antiviral therapy. To our knowledge, no research has been conducted to explore which is the most appropriate criterion. For clinical trials, exclusion criteria should not only exclude factors that can potentially affect clinical outcomes but guarantee enrolling eligible patients as much as possible. This study showed that both PFS and OS were similar between HCC patients with low and high baseline HBV loads when they received antiviral treatments. If HCC patients with high baseline HBV loads are excluded from clinical trials due to perceived risks that HBV may have negative impacts on the survival of patients, our results may alleviate this concern.

Investigators may concern that high baseline HBV loads can adversely affect the prognosis of HCC patients since previous studies have reported that HCC patients with high HBV loads had worse survival than those with low HBV loads in different treatment modalities such as hepatectomy, TACE, sorafenib and so on.^{20–22} However, these studies did not further analyze whether antiviral treatments could eliminate the adverse effects of high HBV loads. Till now, the validity of this concern has barely been validated. Takafumi et al have reported that chronic viral hepatitis does not significantly compromise the efficiency of anticancer agents or adversely affect the survival in Phase I clinical trials.²³ They also found that there was no significant difference in the rates of hepatitis virus reactivation and adverse events between patients with negative and positive hepatitis virus. Besides, the efficiency and feasibility of nivolumab was similar in patients with and without viral hepatitis in CheckMate 040.¹⁰ We specifically compared the survival of HCC patients with low and high HBV loads when they were treated with antiviral drugs in reported studies. With antiviral treatments, the prognosis was comparable between patients with HBV loads <2000 IU/mL and those with HBV loads \geq 2000 IU/mL after undergoing hepatectomy for early-stage HBV-related HCC.²⁴ For HCC patients receiving sorafenib, antiviral treatments could eliminate the adverse impacts of high HBV loads on survival.²⁵ Peter et al found that antiviral therapy can provide benefits for HCC patients in terms of survival, liver function and adverse events.²⁶ Similarly, HCC patients receiving TACE or anti-PD-1 immunotherapy can also benefit from antiviral therapy.²⁷ According to above findings, it can be inferred that antiviral drugs can eliminate the adverse effects of high HBV loads on the survival of HCC patients. Thus, receiving antiviral treatment is necessary for patients with HBV-related HCC in clinical trials. However, baseline HBV DNA levels may not be reasonable exclusion criteria, which can decrease accrual rates of trials.

This study has several limitations except for its retrospective nature. First, this study focused on the impacts of HBV loads on survival outcomes but did not further evaluate whether the rates of HBV reactivation and adverse events differed

among HCC patients with different viral loads. It has been reported that HBV reactivation had no significant association with OS in HCC receiving HAIC with antiviral treatments.²⁸ Nucleoside analogs can inhibit hepatitis activity and reverse liver function, which improves patients' tolerance to anticancer therapy and survival.²⁹ Second, HBV loads were only measured at baseline, while the changes in viral loads were not regularly monitored. Whether the decline of HBV loads affects clinical outcomes needs further exploration. The purpose of this study focused on expanding clinical trial enrollment by evaluating whether baseline HBV loads could affect the survival of HCC patients with antiviral treatments. Third, proper eligibility criteria remain to be explored for HCC patients with hepatitis C virus infection.

In conclusion, antiviral treatments could eliminate the adverse impacts of high baseline HBV loads on the survival of HCC patients. Simplified eligibility criteria can be adopted for HCC patients with HBV infection where regular antiviral therapy should be enough. Strict criteria for baseline HBV loads may compromise the efficiency and generalizability.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. This research was approved by the institutional review board of Sun Yat-sen University Cancer Center. The study used retrospective anonymous clinical data that were obtained after each patient agreed to treatment.

Author Contributions

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

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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