Interaction between hepatitis B virus infection and the efficacy of camrelizumab in combination with apatinib therapy in patients with hepatocellular carcinoma: a multicenter retrospective cohort study

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Background: The interaction between hepatitis B virus (HBV) load and anti-programmed cell death (PD)-1 in combination with (+) antiangiogenic therapy remains controversial, especially for hepatocellular carcinoma (HCC) patients. This study sought to explore the effects of HBV load and antiviral therapy on anti-PD-1+ antiangiogenic therapy, and the rate of HBV reactivation during anti-PD-1+ antiangiogenic treatment.

Methods: We performed a multicenter retrospective cohort study of camrelizumab combined with apatinib (C+A) therapy between January 1, 2019 and January 1, 2021 in patients with unresectable HCC who were seropositive for hepatitis B surface antigen (HBsAg) and received antiviral therapy before C+A involvement. The effects of HBV load and antiviral therapy on C+A and the rate of HBV reactivation during C+A treatment were examined.

Results: Eighty-six patients were included in the analysis. The patients had a mean age of 55 years, and 72 (83.7%) were male. The objective response rates (ORRs) in patients with low (<2,000 IU/mL) and high (≥2,000 IU/mL) baseline HBV deoxyribonucleic acid (DNA) levels were 34.5% and 32.2%, respectively (χ^2=0.046; P=0.829), while the disease control rates (DCRs) were 67.3% and 80.6%, respectively (χ^2=1.762; P=0.184). The results of the univariate and multivariate analyses showed that the baseline HBV DNA level did not affect PD. Additionally, none of the 86 patients suffered from HBV reactivation or HBV-related hepatic impairment with continuous antiviral treatment, regardless of nucleos(t)ide analogue (NA) type (F=1.473; P=0.228).

Conclusions: Baseline HBV loads did not affect the tumor responses of HCC patients receiving anti-PD-1+ antiangiogenic therapy. Thus, HBV reactivation should not be a contradiction for anti-PD-1+ antiangiogenic therapy among patients undergoing continuous and effective antiviral treatment.

Keywords: Hepatocellular carcinoma (HCC); hepatitis B virus (HBV); camrelizumab; apatinib; reactivation

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Introduction

Hepatocellular carcinoma (HCC) ranks in the top 3 frequent causes of cancer-related mortality globally and in China (1,2). Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the 2 main risk factors for the development of HCC worldwide, particularly in Eastern Asia and sub-Saharan Africa (3). Despite antiviral treatment being widely applied in the past decade, it has been estimated that HBV infections account for nearly 80% of HCC cases in China (4). Surgery, liver transplantation, and ablation are potentially effective strategies for the early treatment of HCC. Unfortunately, less than 30% of HCC cases can be diagnosed and treated at an early stage, which results in limited treatment options and poor prognosis (5).

For most late-stage HCC patients, the programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) pathway inhibitor, particularly in combination with antiangiogenic therapy, have been proven to be optimal regimens for the systemic treatment of HCC (6). One study showed that the new IMbrave150 strategy was superior to that of sorafenib, and reduced the risk of death by 42%. As a result, the atelizumab in combination with bevacizumab regimen became the first-line treatment for patients with advanced HCC (7). Additionally, research on the RESCUE showed that camrelizumab combined with apatinib (C+A) had a promising objective response rate (ORR) of 34.3% and a disease control rate (DCR) of 77.1% in advanced HCC patients as a first-line treatment (8). However, the above clinical trials, in which anti-PD-1/PD-L1 was used in combination with antiangiogenic therapy, excluded patients with pre-existing HBV infection or high HBV loads (≥2,000 IU/mL). Thus, the interaction between HBV load and anti-PD-1/PD-L1+ antiangiogenic therapy remains controversial, especially for HCC patients.

To date, few studies have reported high HBV load as a risk factor for early recurrence and/or poor overall survival (OS) after surgery in HCC patients (9-11). Zhang *et al.* showed that HBV reactivation occurs in a subset of hepatitis B surface antigen (HBsAg)-positive cancer patients undergoing anti-PD-1 or anti-PD-L1 immunotherapy (12). However, Sun *et al.* found that HBV loads did not compromise the clinical outcomes of HCC patients receiving anti-PD-1 inhibitors (13). To explore the effects of HBV load and antiviral therapy on anti-PD-1+ antiangiogenic therapy and the rate of HBV reactivation during anti-PD-1+ antiangiogenic treatment, we performed a retrospective cohort study of HBV-associated HCC patients in China. To our knowledge, this report is novel, as it examines the interaction between HBV infection and anti-PD-1+ antiangiogenic therapy. We wish to share our experience with developing countries in which the majority of HCC cases are also associated with chronic HBV infection. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-3020).

Methods

Study design and patients

We conducted a multicenter retrospective cohort study of C+A therapy in patients with unresectable HCC who were seropositive for HBsAg and accepted antiviral therapy before C+A involvement. Consecutive patients referred to the following hospitals between January 1, 2019 and January 1, 2021 were enrolled in this study: (I) Nanfang Hospital, Southern Medical University; (II) the First affiliated Hospital, School of Medicine, Zhejiang University; (III) the First Affiliated Hospital of Sun Yat-sen University; (IV) the Second Affiliated Hospital of Guangzhou Medical University; and (V) Shunde Hospital, Southern Medical University. A total of 149 patients were screened for eligibility.

To be eligible to participate in this study, patients had to meet the following inclusion criteria: (I) have a pathological diagnosis of HCC; (II) be in stage B/C according to the Barcelona Clinic Liver Cancer (BCLC) staging system (14) and be unable to tolerate or have refused surgery, ablation, radiation, or liver transplantation; (III) have received at least 2 cycles of anti-PD-1 therapy; (IV) have Child-Pugh (C-P) A or B liver function; (V) be seropositive for HBsAg and have received antiviral therapy as regular therapy before "C+A" therapy. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had received apatinib or anti-PD-1 therapy previously;

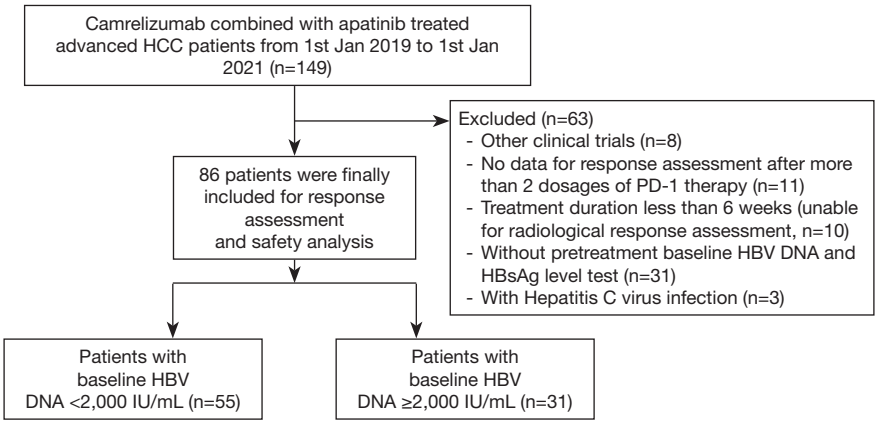

Figure 1 Flowchart of patient selection.

(II) were pregnant or breast feeding women; (III) currently had or had a history of another malignant tumor; (IV) had positive viral markers, including immunoglobulin M antibodies to the hepatitis A virus, HCV, or hepatitis E virus, immunoglobulin G antibodies to the hepatitis D virus or antibodies to the human immunodeficiency virus (HIV). Ultimately, 86 patients with complete data were included in this study. *Figure 1* shows a flowchart of our patient selection procedure.

The reliability of this study was evaluated by calculating the power of the test based on the sample size and research outcomes. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The Ethical Committee of Nanfang Hospital, Southern Medical University (NFEC-2019-069) granted approval for this study, and written informed consent was obtained from each patient before the procedure.

Treatment and assessment

We described the dosage of PD-1 inhibitor and apatinib therapy in our previous study (15,16). Briefly, 200 mg of camrelizumab was administered intravenously every 3 weeks, and 250 mg of Apatinib was administered orally daily.

Patients' demographic and clinical data were collected before C+A therapy. Data were collected in relation to patients' age, gender, alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), albumin (ALB), platelet count (PLT), total bilirubin , alpha-fetoprotein (AFP), BCLC stage, Eastern Cooperative Oncology Group performance, C-P score, tumor size and number, vascular invasion, and extrahepatic metastasis. An albumin-bilirubin (ALBI) score was calculated for each patient using the following formula: ALBI score = (log10 bilirubin × 0.66) + (albumin × −0.085), where bilirubin is in μmol/L and albumin in g/L. All patients underwent a computed tomography (CT) or magnetic resonance imaging (MRI) at the baseline, 6–12 weeks after treatment initiation, and about 3–6 months thereafter. Serological markers for HBV infection, including HBsAg, hepatitis B surface antibody (anti-HBs), antibody to hepatitis B core antigen anti-HBc), hepatitis B e-antigen (HBeAg), and antibody to hepatitis B e-antigen (anti-HBe) and HBV deoxyribonucleic acid (DNA), were also tested at each follow-up visit. The serum HBV DNA level was measured with the Cobras Taqman HBV Kit (Roche Diagnostics; lower limit of detection: 20 IU/mL).

The modified response evaluation criteria in solid tumors (mRECIST) (17) were used to evaluate tumor responses. Under the mRECIST, the responses include: (I) complete response (CR): target lesions disappeared according to the enhanced imaging in the arterial phase; (II) partial response (PR): the diameter of the target lesions reduced by ≥30% according to the enhanced imaging in the arterial phase; (III) stable disease (SD): the diameter of the target lesions did not reduce to that in PR and did not increase to that in disease progression; (IV) progressive disease (PD): the total increase of the diameter of the target lesions (enhanced arterial phase) was ≥20% compared to that of the baseline value, or new lesions appeared. To reduce bias, tumor response was assessed by 2 experienced doctors with over 5 years' experience. HBV reactivation was defined according to the American Association for the Study of Liver Diseases

2018 whereby: (I) a ≥2 log (100-fold) increase in HBV DNA compared to the baseline level; (II) a ≥3,000 IU/mL in increase in HBV DNA in a patient with a previously undetectable level. HBV-related hepatitis was defined as a 3-fold or greater increase in serum ALT level that exceeded the reference range (58 U/L) or an absolute increase in serum ALT to more than 100 U/L accompanying or following HBV reactivation.

Statistical analysis

The statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL). Categorical variables are expressed as counts and percentages. In accordance with normal distribution, continuous variables are expressed as mean ± standard deviation (SD). In accordance with non-normal distribution, non-continuous variables are expressed as median (minimum, maximum). Qualitative differences between the subgroups were analyzed using χ^2 tests or Fisher's exact test for categorical parameters. Survival data were calculated using the Kaplan-Meier method. Log-rank tests were used in the univariate analysis, and variables with a P value less than 0.1 were entered into the multivariate analysis. The multivariate analysis was performed using a Cox's proportional hazard regression model. Values of P<0.05 were considered significant.

Results

Patients

Between January 2019 and January 2021, a total of 149 HCC patients received C+A therapy (see *Figure 1*). The data collection cutoff time was April 30, 2021. Sixty-three patients were excluded, as they were participating in other clinical trials (n=8), were co-infected with HCV (n=3), had incomplete data (n=42), or had a follow-up period <6 weeks (n=10). A total of 86 patients were included in the analysis. The power was 0.91, which indicated a sufficient sample size and credible results.

Table 1 shows the clinical characteristics of the patients at the baseline. Patients were predominantly male (n=72, 83.7%), and had a mean age of 55 years ; 74.4% (64/86) patients had BCLC C, and 50% (43/86) had ALBI grade 1. All patients were on antiviral prophylaxis before commencing the C+A therapy, and the most commonly used agents were tenofovir alafenamide fumarate (TAF; n=38, 44.2%) and entecavir (ETV; n=32, 37.2%). At the baseline, 55 patients (64.0%) had a low HBV DNA level (baseline viral load <2,000 IU/mL), while 31 patients (36.0%) had a high HBV DNA level (baseline viral load ≥2,000 IU/mL).

Tumor responses

Tumor responses are shown in *Table 2*. Of all the included patients, 1 achieved a CR (1.2%), 28 achieved a PR (32.5%), and 33 patients had SD (27.9%), resulting in an ORR of 33.7% and a DCR of 72.1%. The subgroup analysis revealed that ORRs in patients with low and high baseline HBV DNA levels were 34.5% and 32.2%, respectively (χ^2=0.046; P=0.829), while the DCRs were 67.3% and 80.6%, respectively (χ^2=1.762; P=0.184).

Correlations between the baseline variables and progressive disease

To evaluate whether baseline variables, especially the HBV DNA level, affected PD, a logistical regression analysis was conducted. The univariate regression analysis identified the following factors as affecting PD: portal vein tumor thrombus (OR 3.336, 95% CI, 1.374–8.005; P=0.008), AFP level ≥400 ng/mL (OR 2.312, 95% CI, 0.989–5.406; P=0.053), and ALBI grade 2/3 (P=0.003). We then entered these significant factors into our multivariate analysis, and found that portal vein tumor thrombus (OR 3.761, 95% CI, 1.471–9.617; P=0.006) and ALBI grade 2/3 (P=0.021) were the only 2 independent predictive factors of PD (see *Table 3*).

Effects of anti-PD-1 in combination with antiangiogenic therapy on HBV DNA and hepatitis

During the follow-up period, none of the 86 patients suffered from HBV reactivation. As *Figure 2* shows, only 3 patients suffered higher HBV DNA levels at the end of the follow-up period than at the baseline (2 received ETV, and 1 received TAF). There was no statistical difference in HBV DNA reduction among the 4 nucleos(t)ide analogue (NA) groups (F=1.473; P=0.228). Similarly, there was also no statistical difference in HBsAg reduction among the 4 NA groups (F=0.770; P=0.514). None of the treated patients achieved HBsAg or HBeAg seroclearance at the end of follow-up period (see *Figure 3*). Ten (11.6%) patients experienced ALT elevation; however, all of these were considered cases of immune-related hepatitis, as no patient suffered from HBV reactivation with the continuous

Table 1 Baseline characteristics of the 86 advanced HCC patients receiving camrelizumab in combination with apatinib therapy

Characteristics	All patients (n=86)
Gender, n (%)	
Male	72 (83.7)
Female	14 (16.3)
Age (y)$^{\Delta}$	54.5±12.1
BCLC stage, n (%)	
B	22 (25.6)
C	64 (74.4)
Child-Pugh class, n (%)	
A	64 (74.4)
B	22 (25.6)
ECOG performance, n (%)	
0	1 (1.2)
1	54 (62.8)
2	31 (36.0)
Portal vein tumor thrombus, n (%)	
Yes	40 (46.5)
No	46 (53.5)
Extrahepatic metastasis, n (%)	
Yes	20 (23.3)
No	66 (76.7)
Tumor number, n (%)	
<3	39 (45.3)
≥3	47 (54.7)
Largest tumor diameter (cm)	7.4 (1.0, 17.8)
α-Fetoprotein level, n (%)	
<400 ng/mL	42 (48.8)
≥400 ng/mL	44 (51.2)
ALT (U/L)*	30.0 (5.0, 216.0)
AST (U/L)*	42.0 (9.0, 231.0)
Albumin (g/L)$^{\Delta}$	37.1±5.3
Total bilirubin (mmol/L)*	13.6 (5.3, 78.7)
PLT (10^9/L)*	158.0 (35.0, 556.0)
PT (s)*	11.6 (9.7, 142.0)
ALBI grade, n (%)	
1	43 (50.0)
2	37 (43.0)
3	6 (7.0)
HBV DNA, n (%)	
<2,000 IU/mL	55 (64.0)
≥2,000 IU/mL	31 (36.0)
HBsAg (IU/mL)*	219.8 (1.71, 7,379.0)
HBeAg, n (%)	
Positive	18 (2.9)
Negative	68 (79.1)
Anti-viral therapy, n (%)	
ETV	32 (37.2)
TDF	11 (12.8)
TAF	38 (44.2)
Others	5 (5.8)

$^{\Delta}$, normal distribution (mean ± standard deviation); *, non-normal distribution [median, (minimum, maximum)]. HCC, hepatocellular carcinoma; BCLC, Barcelona-Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet count; PT, prothrombin time; others, LDV or LAM in combination with ADV; ALBI, albumin-bilirubin grade = (log10 bilirubin × 0.66) + (albumin × −0.085); ETV, entecavir; TDF, tenofovir; TAF, tenofovir alafenamide fumarate; LDV, telbivudine; LAM, lamivudine; ADV, adefovir.

administration of antiviral therapy.

Discussion

In the current study, we explored both the effects of HBV load and antiviral therapy on anti-PD-1+ antiangiogenic therapy and the rate of HBV reactivation during anti-PD-1+ antiangiogenic treatment. Our findings showed that baseline HBV loads did not affect the tumor responses of anti-PD-1+ antiangiogenic treated HCC patients. However, we also proved that no HCC patient receiving continuous antiviral treatment, regardless of the type of NA, suffered from HBV reactivation or HBV-related hepatitis.

Table 2 Best tumor responses of patients with low and high baseline HBV DNA level

Tumor response	All patients (n=86), n (%)	Baseline HBV DNA <2,000 IU/mL (n=55), n (%)	Baseline HBV DNA ≥2,000 IU/mL (n=31), n (%)
CR	1 (1.2)	1 (1.8)	0
PR	28 (32.5)	18 (32.7)	10 (32.2)
SD	33 (38.4)	18 (32.7)	15 (48.4)
PD	24 (27.9)	18 (32.7)	6 (19.4)
ORR (CR + PR)$^{\Delta}$	29 (33.7)	19 (34.5)	10 (32.2)
DCR (CR + PR + SD)*	62 (72.1)	37 (67.3)	25 (80.6)

$^{\Delta}$, Pearson χ^2=0.046, P=0.829; *, Pearson χ^2=1.762, P=0.184. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

As reported, viral infection could affect the clinical prognosis of anti-PD-1 therapy in gastric and anal squamous cell carcinoma (18,19). It may be that viral antigens interfere with the anti-tumor effects of anti-PD-1 in the tumor immune microenvironment (TME). However, a sub-study of the Acquired Immunodeficiency Syndrome Malignancy Consortium-095 Study recently reported that anti-PD-1 alone had no effect on HIV-latency or the latent HIV-reservoir (20). More importantly, Sun *et al.* (13) found no significant association between HBV loads and survival in HCC patients. Based on the above findings, the current results as to whether baseline viral infection interacted with antiviral treatments, especially in HCC patients, remain controversial. Unfortunately, while a substantial number of patients were HBV-infected both in the IMbrave150 and RESCUE studies (7,8), the question of whether HBV load affects the efficacy of the anti-PD-1 + antiangiogenesis regimen or the above regimen induces HBV reactivation was not assessed. Additionally, the TMEs are different between anti-PD-1 monotherapy and anti-PD-1+ antiangiogenesis combination therapy patients, as antiangiogenesis therapies could reduce vascular endothelial growth factor–mediated immunosuppression in both tumors and their TMEs and enhance the efficacy of the PD-1 inhibitor by promoting T-cell infiltration in tumors (21). The present study provided evidence that baseline HBV DNA load does not affect the tumor response of anti-PD-1 + antiangiogenesis therapy by constructing a retrospective cohort that included HCC patients who received C+A therapy. HBV infection may have no effect on TMEs, as it might integrate into both hepatocytes and tumor cells, and as a result, the anti-tumor ability of anti-PD-1 might not depend on HBV-associated immune attacks but on other carcinogenetic processes (22).

Another important finding of this study was that anti-PD-1+ antiangiogenesis therapy had no effect on HBV reactivation and HBV-related hepatic impairment with continuous antiviral treatment, regardless of the NA type. With the objective of "ending viral hepatitis", China has entered an era in which the application of antiviral treatments is widespread (23,24). Accordingly, all the patients included in this cohort were on antiviral prophylaxis before commencing C+A treatment, and the most commonly used agents were TAF and ETV. Consequently, we did not observe any cases of HBV reactivation or HBV-related hepatic impairment during the follow-up period, and our incidence rates of HBV reactivation differed to those reported by Zhang *et al.* (12) (1.6%) and Sun *et al.* (13) (1.4%). HBV reactivation induced by anti-PD-1 might occur through the following mechanisms: (I) anti-PD-1 therapy might destroy hepatocytes and lead to the release of a previously latent virus (25); (II) the antiviral function of HBV-specific CD8+ T cells might be partially improved by the blocking of the PD-1 axis (26); or (III) the proliferation of T regulatory cells (Tregs) might also be promoted, leading to increased immunosuppression (27). Based on our findings, we suggest that HCC patients with positive HBsAg receive antiviral prophylaxis before anti-PD-1+ antiangiogenesis therapy. However, HBV reactivation must be closely monitored.

Our study had several limitations. First, this study was retrospectively designed; however, the objective endpoints (especially the imaging data for the tumor response assessments) were elaborately and integrally recorded. Second, 63 patients were excluded from this study, which may have reduced the study's statistical power; however,

Table 3 Univariate and multivariate analysis of baseline variables affecting DCR

Factors	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Gender: M/F	5.200	0.702–38.517	0.107			
Age (y)	1.008	0.974–1.043	0.646			
BCLC stage: B/C	0.561	0.245–1.283	0.171			
Child-Pugh class: B/A	2.651	0.790–8.895	0.114			
ECOG performance			0.500			
0[&]						
1	0.000	–	0.979			
2	0.617	0.277–1.378	0.239			
Portal vein tumor thrombus: yes/no	3.336	1.374–8.005	0.008	3.761	1.471–9.617	0.006
Extrahepatic metastasis: yes/no	1.193	0.473–3.007	0.708			
Tumor number: ≥3/<3	1.088	0.487–2.428	0.838			
Largest tumor diameter (cm)	0.969	0.881–1.066	0.515			
α-Fetoprotein level: ≥400/<400 ng/mL	2.312	0.989–5.406	0.053	1.944	0.816–4.631	0.134
ALT (U/L)	1.006	0.995–1.017	0.324			
AST (U/L)	0.996	0.985–1.007	0.440			
Albumin (g/L)	1.032	0.957–1.113	0.412			
Total bilirubin (mmol/L)	0.972	0.921–1.026	0.309			
PLT (10^9/L)	0.998	0.994–1.003	0.522			
PT (s)	0.815	0.573–1.159	0.254			
ALBI grade			0.003			0.021
1[&]						
2	2.879	1.094–7.580	0.032	3.420	1.261–9.278	0.016
3	7.774	2.354–25.679	0.001	4.637	1.357–15.846	0.014
Baseline HBV DNA: ≥2,000/<2,000 IU/mL	1.678	0.666–4.229	0.272			
HBsAg (IU/mL)	1.000	0.999–1.000	0.119			
HBeAg: positive/negative	3.286	0.772–13.983	0.107			
Anti-viral therapy			0.506			
ETV[&]						
TDF	0.570	0.125–2.603	0.468			
TAF	0.739	0.300–1.819	0.510			
Others	1.813	0.499–6.594	0.366			

[&], used as the reference category. DCR, disease control rate; BCLC, Barcelona-Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet count; PT, prothrombin time; others, LDV or LAM in combination with ADV; ALBI, albumin-bilirubin grade = (log10 bilirubin × 0.66) + (albumin × −0.085); ETV, entecavir; TDF, tenofovir; TAF, tenofovir alafenamide fumarate; LDV, telbivudine; LAM, lamivudine; ADV, adefovir.

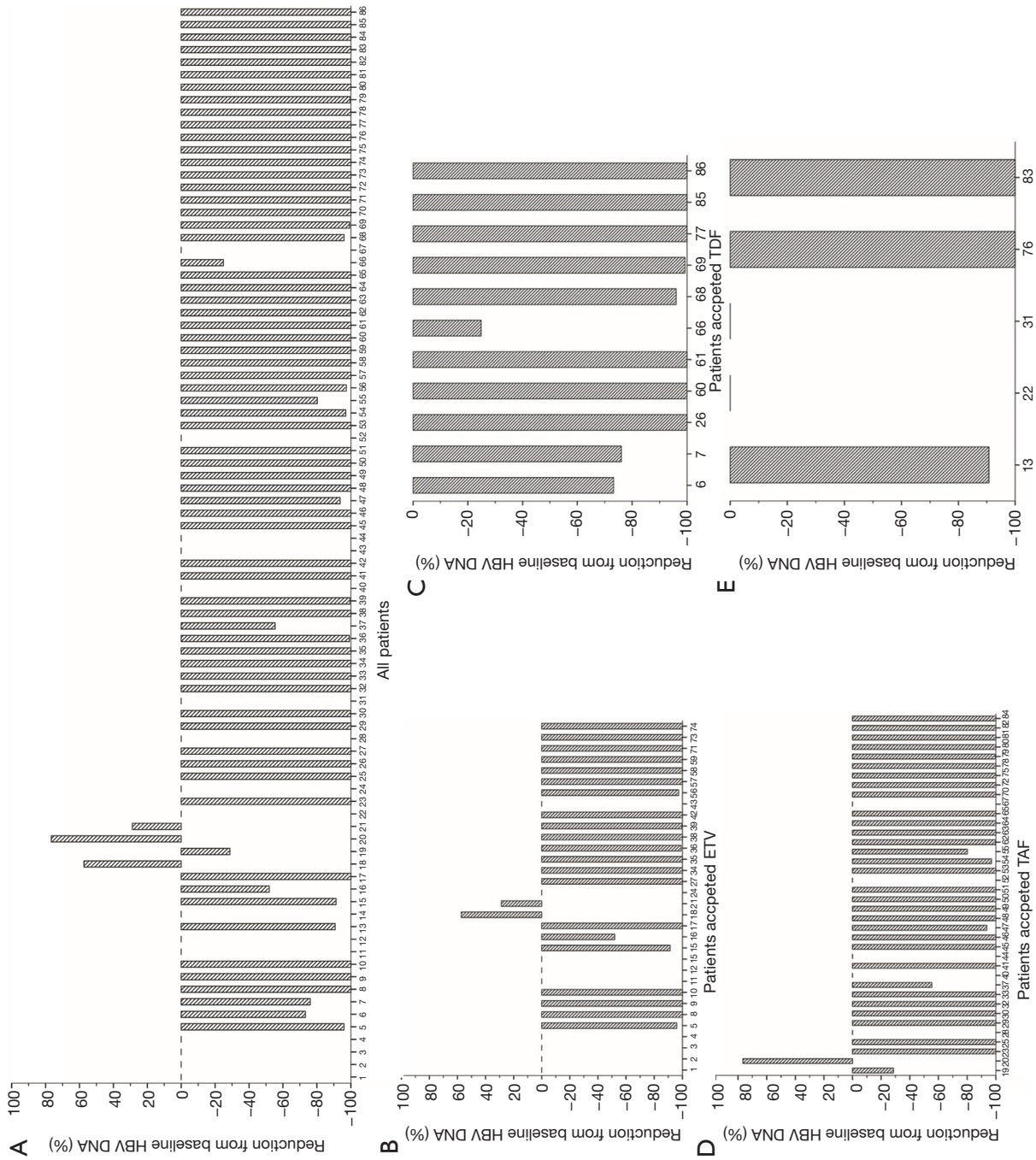

Figure 2 HBV DNA reduction rate compared to the baseline (R = HBV DNA at the end of the follow-up period/baseline HBV DNA ×100%). (A) Data of all patients; (B) data of patients treated with ETV; (C) data of patients treated with TDF; (D) data of patients treated with TAF; (E) data of patients treated with other antiviral drugs, such as LDV or LAM, in combination with ADV. HBV, hepatitis B virus; ETV, entecavir; TAF, tenofovir alafenamide fumarate; LDV, relbivudine; LAM, lamivudine; ADV, adefovir.

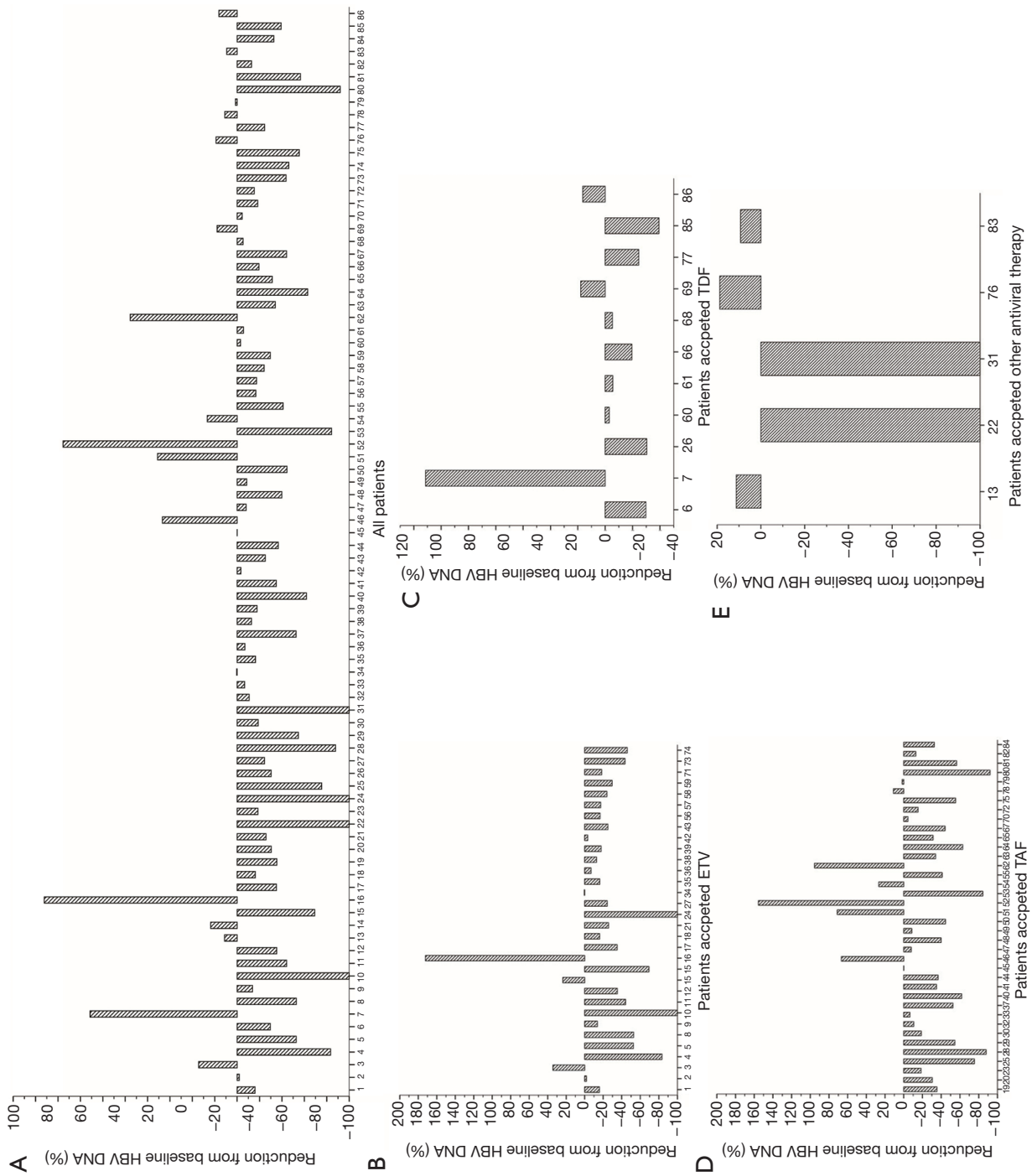

Figure 3 HBsAg reduction rate compared to the baseline (R = HBsAg at the end of the follow-up period/baseline HBsAg ×100%). (A) Data of all patients; (B) data of patients treated with ETV; (C) data of patients treated with TDF; (D) data of patients treated with TAF; (E) data of patients treated with other antiviral drugs, such as LDV or LAM, in combination with ADV. HBsAg, hepatitis B surface antigen; ETV, entecavir; TAF, tenofovir alafenamide fumarate; LDV, telbivudine; LAM, lamivudine; ADV, adefovir.

the reliability of this study was evaluated by calculating the power of the test. Third, survival data was not included in the present study, as only a fraction of the included patients died, and the follow-up period was not long enough to calculate OS. Our future research will expand the sample size and focus on the subgroup analysis of survival.

In conclusion, our findings are important, as they provide evidence that baseline HBV loads do not affect the tumor response of anti-PD-1+ antiangiogenic treated HCC patients. Further, HBV reactivation should not be a contradiction for anti-PD-1+ antiangiogenic therapy among patients undergoing continuous and effective antiviral treatment. As this study used non-randomized retrospective observational data, it only provides limited evidence that these drugs are efficacious and safe. Without further evidence-based confirmation, these data should not be taken as non-biased or used to inform clinical decisions. Future prospective studies with longer follow-up periods, larger sample sizes, and different anti-PD-1+ antiangiogenic strategies need to be conducted.

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Footnote

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Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-3020

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The Ethical Committee of Nanfang Hospital, Southern Medical University (NFEC-2019-069) granted approval for this study, and written informed consent was obtained from each patient before the procedure.

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