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ORIGINAL ARTICLE

Retrospective Study

Impact of baseline hepatitis B virus viral load on the long-term prognosis of advanced hepatocellular carcinoma treated with immunotherapy

Di Pan, Hao-Nan Liu, Zhi-Yuan Yao, Xiao-Xiao Chen, Yu-Qi Li, Jing-Jing Zhu, Zheng-Xiang Han, Xiao-Bing Qin

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Abstract

BACKGROUND

Although the combination of lenvatinib and PD-1 inhibitors has become the standard regimen for the treatment of advanced hepatocellular carcinoma (HCC), real data on the impact of baseline hepatitis B virus (HBV)-DNA levels on the clinical efficacy of this regimen is still limited.

AIM

To evaluate the effectiveness of camrelizumab combined with lenvatinib in patients with HCC at varying levels of HBV-DNA.

METHODS

One hundred and twenty patients with HCC who received camrelizumab and lenvatinib treatment were categorized into two cohorts: HBV-DNA ≤ 2000 (n = 66) and HBV-DNA > 2000 (n = 54). The main outcomes measured were overall survival (OS) and progression-free survival (PFS), while additional outcomes included the rate of objective response rate (ORR), disease control rate (DCR), and any negative events. Cox proportional hazards regression analysis revealed independent predictors of OS, leading to the creation of a nomogram incorporating these variables.

RESULTS

The median PFS was 8.32 months for the HBV-DNA ≤ 2000 group, which was similar to the 7.80 months observed for the HBV DNA > 2000 group (P = 0.88).

Likewise, there was no notable variation in the median OS between the two groups, with durations of 13.30 and 14.20 months respectively (P = 0.14). The ORR and DCR were compared between the two groups, showing ORR of 19.70% *vs* 33.33% (P = 0.09) and DCR of 72.73% *vs* 74.07% (P = 0.87). The nomogram emphasized the importance of antiviral treatment as the main predictor of patient results, with portal vein tumor thrombus and Barcelona Clinic Liver Cancer staging following closely behind.

CONCLUSION

The clinical outcomes of patients with HBV-associated HCC treated with camrelizumab in combination with lenvatinib are not significantly affected by HBV viral load.

Key Words: Hepatitis B virus; Hepatocellular carcinoma; Camrelizumab; Lenvatinib; Efficacy

Core Tip: In this manuscript, we revisited the different clinical outcomes of hepatocellular carcinoma (HCC) patients treated with camrelizumab in combination with lenvatinib, explored the different clinical outcomes of HCC patients with different baseline hepatitis B virus viral load, and developed a predictive model with nomograms based on the results of COX regression.

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INTRODUCTION

Globally, primary liver cancer ranks sixth in incidence and third in mortality, with hepatocellular carcinoma (HCC) representing the most common pathology[1,2]. Notably, over half of these cases arise in China, predominantly attributable to hepatitis B virus (HBV) infection, underscoring its significant burden on morbidity and mortality[3,4]. Despite advancements in HCC treatment, patients continue to face limited therapeutic options and a bleak prognosis[5]. The challenge is compounded by late-stage diagnoses, depriving many patients of curative interventions[6]. Consequently, non-surgical modalities such as immunological and targeted therapies assume paramount importance in HCC management[7].

Lenvatinib, a tyrosine kinase inhibitor taken by mouth, has anti-cancer and anti-blood vessel growth effects by blocking specific receptors like vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptors, and other important pathways[8]. Notably, based on the Reflect study[9], lenvatinib received approval from the European Medicines Agency, the US Food and Drug Administration, and the National Medical Products Administration in 2018 as a first-line therapy for advanced HCC, alongside sorafenib[10]. Additionally, findings from a global phase 3 clinical trial conducted by Finn *et al*[11] revealed that the combination of PD-1 inhibitors with anti-angiogenic agents yielded promising outcomes in unresectable HCC, boasting a 1-year survival rate of 67.2% and an objective response rate (ORR) of 33.2%. Subsequently, numerous trials exploring the synergy between programmed death receptor 1 (PD-1/PD-L1) inhibitors and anti-angiogenic targeted therapies have emerged, gaining approval as first-line systemic therapies for advanced HCC[12,13].

Camrelizumab, a PD-1/PD-L1 inhibitor, has garnered approval from the State Food and Drug Administration for HCC treatment[14]. Within tumor microenvironments, the PD-1/PD-L1 axis impedes effector T cell function, dampens anti-tumor immune responses, and fosters tumor progression[15]. Presently, the combination of camrelizumab with lenvatinib has demonstrated efficacy as both first- and second-line therapies for patients with HCC. Results from the RESCUE study indicated an ORR of 34.3% and a progression-free survival (PFS) of 5.7 months among patients with advanced HCC treated with camrelizumab in combination with lenvatinib[16].

However, the enrollment criteria for many studies investigating PD-1/PD-L1 inhibitors in combination with targeted therapies often stipulate a requirement for HBV-DNA viral load normalization and HBsAg and HBeAg conversion. Consequently, the impact of HBV-DNA viral load on the efficacy of non-targeted combinations remains contentious.

The results from the Chinese subgroup analysis of the IMbrave150 study[11] were unveiled at the American Society of Clinical Oncology 2021. Notably, the median overall survival (OS) for patients receiving atilizumab combined with bevacizumab (T + A) regimen and sorafenib monotherapy stood at 19.2 months and 13.4 months, respectively. Furthermore, the PFS for these groups was recorded at 6.9 months and 4.3 months, respectively. Intriguingly, the median OS for the Chinese subgroup surged to 24.0 months, signifying a substantial extension in survival duration for patients grappling with intermediate and advanced HCC. This phenomenon could potentially be attributed to the heightened disease burden of patients with HBV-associated HCC in China, where immune checkpoint inhibitors might concurrently

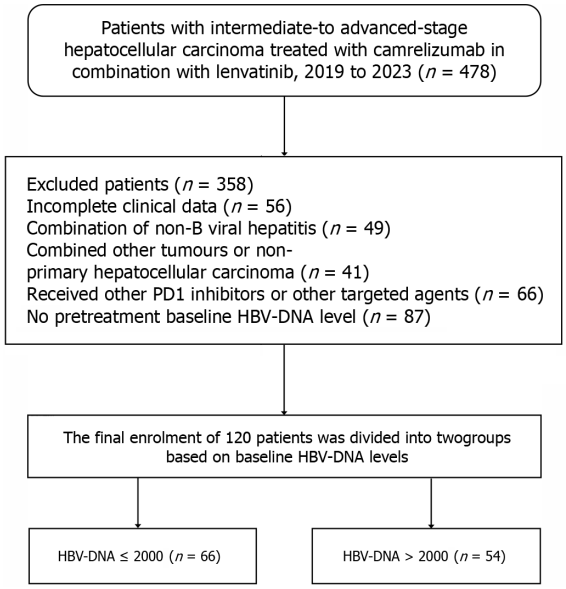

Figure 1 Flow diagram showing the patients with infiltrative hepatocellular carcinoma enrolled in the study. HBV: Hepatitis B virus.

contribute to antiviral therapy while exhibiting their anti-tumor mechanisms.

Kubo *et al*[17] were the pioneers in reporting that a high viral load served as an independent risk factor for HCC recurrence after hepatectomy among patients with HBV-associated HCC. Subsequently, several studies corroborated these findings[18,19]. However, conflicting results emerged from other studies[20,21], which failed to establish a significant correlation between baseline HBV-DNA levels and OS or PFS in patients with HCC treated with immunosuppressive agents.

While the administration of camrelizumab in combination with lenvatinib has become a standard regimen for advanced HCC treatment, real-world data regarding the impact of HBV on the efficacy of this regimen in clinical settings remain scarce. Thus, there is a pressing need to delve deeper into this aspect to garner more evidence for informed clinical practice. Motivated by this gap, we embarked on a retrospective clinical study to examine the influence of HBV viral load on the long-term prognosis of patients with HCC treated with camrelizumab in combination with lenvatinib.

MATERIALS AND METHODS

Design of the study and patients

From January 2019 to January 2023, medical records were reviewed for patients with HCC who received camrelizumab and lenvatinib in conjunction.

A total of 461 patients meeting specific criteria were included in the study, including having a confirmed diagnosis of HCC, being at least 18 years old at diagnosis, having information on hepatitis viral infection available, having at least one measurable lesion, receiving at least two treatment cycles, being classified as Child-Pugh class A or B, having a Barcelona Clinic Liver Cancer (BCLC) staging of stage B or C, and having an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 2 or lower.

The criteria for exclusion included: lack of HBV DNA testing before treatment, no tumor visualization within 6 wk before starting anti-PD-1 therapy, having other cancers or non-primary liver cancer at the same time, being infected with hepatitis C or other hepatitis viruses, incomplete medical records, and using other PD-1 inhibitors or different targeted medications. Ultimately, 120 patients were included for analysis. Real-time viral polymerase chain reaction was utilized to evaluate the HBV viral load.

Figure 1 illustrates the process of the study. This retrospective study obtained approval from the Ethics Review Committee and adhered to the principles outlined in the Declaration of Helsinki. Given the retrospective nature of the study, the requirement for written informed consent was waived.

Definitions

As per the 2018 hepatitis B guidelines established by the American Association for the Study of Liver Diseases, HBV reactivation is delineated by three criteria: (1) a ≥ 2 Log (100-fold) increase in HBV DNA in comparison to baseline levels; (2) the presence of previously undetectable HBV DNA in patients with HBV DNA levels ≥ 3 Log (1000) IU/mL (attributable to fluctuating HBV DNA levels); or (3) HBV DNA levels ≥ 4 Log (10000) IU/mL in the absence of baseline levels [22]. Hepatic impairment, as defined by the Common Terminology Criteria for Adverse Events version 5.0, is characterized by alanine aminotransferase or aspartate aminotransferase levels that are ≥ 5 times the upper limit of normal.

Grouping and treatment protocol

HBV-DNA testing was conducted within two weeks before initiating treatment with lenvatinib in combination with camrelizumab. Patient grouping basis for grouping is shown in previous studies[23], with a cut-off value of 2000 IU/mL (categorized as > 2000 IU/mL and ≤ 2000 IU/mL).

Camrelizumab was administered intravenously at a dosage of 200 mg every three weeks. Lenvatinib was prescribed at a dosage of 8 mg daily (two 4 mg capsules) for patients weighing less than 60 kg and 12 mg daily (three 4 mg capsules) for those weighing 60 kg or more.

Assessment

Following initial chest computed tomography or upper abdominal magnetic resonance imaging enhancement scans, patients underwent repeat scans every six to eight weeks. Long-term treatment efficacy was assessed using OS—the duration from treatment initiation to death from any cause—and PFS, defined as the time from treatment start to disease progression or death. Short-term efficacy was evaluated using RECIST 1.1 and mRECIST, assessing complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), ORR and disease control rate (DCR). Adverse events (AEs) were meticulously documented and evaluated according to the National Cancer Institute's CTCAE version 5.0.

Statistical analysis

Statistical analyses were performed using R software version 4.2.0, with categorical data represented by counts and percentages. The median OS and PFS were estimated using the Kaplan-Meier method. Variables showing *P*-values less than 0.05 in univariate Cox regression analyses were included in subsequent multivariate analyses to identify independent prognostic factors for PFS and OS. An OS nomogram prediction model was developed based on these factors. The nomogram was developed and validated at 9 and 12 months and compared against actual outcomes. All significance tests were two-sided, with *P*-values of < 0.05 considered statistically significant.

RESULTS

Patient characteristics

The retrospective study comprised 120 patients diagnosed with BCLC stage B or C HCC who received camrelizumab in combination with lenvatinib from January 2019 to January 2023 (Figure 1). Among these, 66 patients were allocated to the HBV-DNA ≤ 2000 group, while 54 patients fell into the HBV-DNA > 2000 group. The exclusion criteria led to the removal of 358 patients due to various reasons, including incomplete clinical data (n = 56), comorbid non-B viral hepatitis (n = 49), comorbid other tumors or non-primary HCC (n = 41), receipt of other PD-1 inhibitors or targeted drugs (n = 66), and lack of pretreatment baseline HBV-DNA level (n = 87). Patient demographics, including age, sex, body mass index classification, surgical history, smoking status, alcohol abuse, comorbidities such as hypertension and diabetes, presence of cirrhosis, vascular invasion, extrahepatic metastases, ECOG PS, Child–Pugh classification, BCLC staging, laboratory parameters, are detailed in Table 1. No statistically significant differences in baseline characteristics were observed between the two groups (all P > 0.05).

HBV reactivation and hepatic dysfunction following anti-PD-1 immunotherapy

After treatment, HBV reactivation was noted in two patients (1.6%), with one each from the HBV-DNA ≤ 2000 and > 2000 groups. Notably, both patients had baseline HBV-DNA levels recorded, and one did not receive regular antiviral therapy despite a low baseline viral load.

Tumor response

Tumor response outcomes are presented in Table 2. According to RECIST1.1 criteria, none of the patients achieved CR, while 30 patients (25%) attained PR, 56 (46%) exhibited SD, and 34 (28%) experienced PD. The ORR were 20% and 33% (P = 0.09), and DCR were 74% and 73% (P = 0.87) in the low and high baseline HBV-DNA level groups, respectively. As per mRECIST criteria, the ORR were 23% and 41% (P = 0.03), and DCR were 79% and 76% (P = 0.71) in both groups, respectively. Subgroup analyses based on antiviral therapy status revealed superior tumor response in patients receiving antiviral therapy than those not receiving it, irrespective of HBV-DNA levels (ORR: 27% *vs* 20%, P = 0.45; DCR: 27% *vs* 24%, P = 0.74; Table 3).

PFS and OS

According to RECIST 1.1 criteria, the median PFS was 8.32 months (95%CI: 7.33–8.70) in the low-level HBV-DNA group and 7.80 months (95%CI: 5.80–9.71) in the high-level HBV-DNA group, showing no statistically significant difference (P = 0.88; Figure 2A). Similarly, the median OS was 13.30 months (95%CI: 10.1–21.0) in the low-level group and 14.20 months (95%CI: 10.4–15.8) in the high-level group, also not statistically significant (P = 0.14; Figure 2B). Further subgroup analyses of antiviral therapy's impact on PFS and OS demonstrated that median PFS was 7.33 months (5.80–NA) in the group without antiviral therapy compared to 8.32 months (7.28–9.3) in the treated group (Figure 2C). The median OS was 7.8 months (7.1–NA) in the untreated group and 14.7 months (10.6–18) in the treated group (Figure 2D). By the time of follow-up, a total of 81 patients had died, with 41 and 40 deaths in the low-level and high-level HBV-DNA groups, respectively.

Table 1 Baseline characteristics of the hepatitis B virus-DNA > 2000 and hepatitis B virus-DNA ≤ 2000 groups, *n* (%)

Variable	Group		*P* value
	HBV-DNA > 2000, *n* = 54	HBV-DNA ≤ 2000, *n* = 66	
HBV			0.614
Negative	37 (69)	48 (73)	
Positive	17 (31)	18 (27)	
Antiviral therapy			0.068
No	8 (15)	19 (29)	
Yes	46 (85)	47 (71)	
Child Pugh score			0.724
A	22 (41)	29 (44)	
B	32 (59)	37 (56)	
IVPTT			0.595
No	26 (48)	35 (53)	
Yes	28 (52)	31 (47)	
BCLC stage			0.776
B	21 (39)	24 (36)	
C	33 (61)	42 (64)	
Metastasis			0.632
No	31 (57)	35 (53)	
Yes	23 (43)	31 (47)	
AFP			0.271
> 1210	24 (44)	36 (55)	
≤ 1210	30 (56)	30 (45)	
Sex			0.925
Female	20 (37)	25 (38)	
Male	34 (63)	41 (62)	
Age			0.811
< 60	29 (54)	34 (52)	
≥ 60	25 (46)	32 (48)	
BMI			0.413
Low	36 (67)	37 (56)	
Normal	2 (4)	6 (9)	
Obese	1 (2)	4 (6)	
Overweight	15 (28)	19 (29)	
ECOG			0.271
0-1	29 (54)	42 (64)	
2	25 (46)	24 (36)	
Post operative			0.549
No	34 (63)	38 (58)	
Yes	20 (37)	28 (42)	
ALT			0.083
> 40	29 (54)	25 (38)	

≤ 40	25 (46)	41 (62)	
Total bilirubin			0.969
> 34	37 (69)	45 (68)	
≤ 34	17 (31)	21 (32)	
Diabetes			0.832
No	41 (76)	49 (74)	
Yes	13 (24)	17 (26)	
Hypertensive			0.920
No	16 (30)	19 (29)	
Yes	38 (70)	47 (71)	
Cirrhosis			0.753
No	31 (57)	36 (55)	
Yes	23 (43)	30 (45)	
Smoking			0.889
No	37 (69)	46 (70)	
Yes	17 (31)	20 (30)	
Alcohol			0.893
No	35 (65)	42 (64)	
Yes	19 (35)	24 (36)	
Virus reactivation			1.000
No	53 (98)	65 (98)	
Yes	1 (1.9)	1 (1.5)	

Data in brackets represent the percentages of patients. HBV: Hepatitis B virus; BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer; PVTT: Portal vein tumor thrombosis.

Table 2 Tumor response between the hepatitis B virus-DNA ≤ 2000 and hepatitis B virus-DNA > 2000 groups, *n* (%)

	RECIST 1.1		*P* value	mRECIST		*P* value
	HBV ≤ 2000, *n* = 66	HBV > 2000, *n* = 54		HBV ≤ 2000, *n* = 66	HBV > 2000, *n* = 54	
CR	0	0	-	0	0	-
PR	13 (19.70)	17 (31.48)	0.14	15 (22.73)	18 (33.33)	0.20
SD	35 (53.03)	21 (38.89)	0.12	37 (56.06)	23 (42.59)	0.14
PD	18 (27.27)	16 (29.63)	0.78	14 (21.21)	13 (24.07)	0.71
ORR	13 (19.70)	18 (33.33)	0.09	15 (22.73)	22 (40.74)	0.03
DCR	48 (72.73)	40 (74.07)	0.87	52 (78.79)	41 (75.93)	0.71

Data in brackets represent the percentages of patients. HBV: Hepatitis B virus; CR: Complete responds; PR: Partial responds; SD: Stable disease; PD: Progression disease; ORR: Objective responds rates; DCR: Disease control rates.

Univariate and multivariate analyses of PFS and OS

Table 4 summarizes the results of univariate and multivariate Cox proportional risk regression analyses for PFS. Multifactorial Cox proportional risk regression analysis identified BCLC classification [0.55 (0.35–0.87)] and ECOG score [1.92 (1.25–2.96)] as independent prognostic factors for PFS in patients with HCC. Similarly, Table 5 presents the results of unifactorial and multifactorial Cox proportional risk regression analyses for OS. In multifactorial Cox proportional risk regression analysis, alpha-fetoprotein (AFP) level [0.95 (0.56–1.60)], antiviral therapy [0.43 (0.20–0.89)], BCLC classification [2.22 (1.27–3.86)], and portal vein tumour thrombus [2.28 (1.29–4.05)] emerged as independent prognostic factors for OS in patients with HCC. Utilizing these independent prognostic factors, 9-month and 12-month nomogram

Table 3 Subgroup analysis of tumour response according to whether or not they received antiviral therapy, *n* (%)

	Antiviral therapy (no), *n* = 25			Antiviral therapy (yes), *n* = 95		
	HBV-DNA (HBV > 2000), *n* = 8	HBV-DNA (HBV ≤ 2000), *n* = 18	*P* value	HBV-DNA (HBV > 2000), *n* = 46	HBV-DNA (HBV ≤ 2000), *n* = 48	*P* value
PR	2 (29)	3 (17)	0.597	15 (32)	10 (21)	0.220
SD	3 (43)	11 (61)	0.656	18 (38)	24 (50)	0.251
PD	2 (29)	4 (22)	> 0.999	14 (30)	14 (29)	0.947
ORR	2 (29)	3 (17)	0.597	16 (34)	10 (21)	0.149
DCR	5 (71)	14 (78)	> 0.999	35 (74)	34 (71)	0.691
ORR (whole)	5 (20)		-	26 (27)		0.454
DCR (whole)	6 (24)		-	26 (27)		0.735

Data in brackets represent the percentages of patients. HBV: Hepatitis B virus; PR: Partial responds; SD: Stable disease; PD: Progression disease; ORR: Objective responds rates; DCR: Disease control rates.

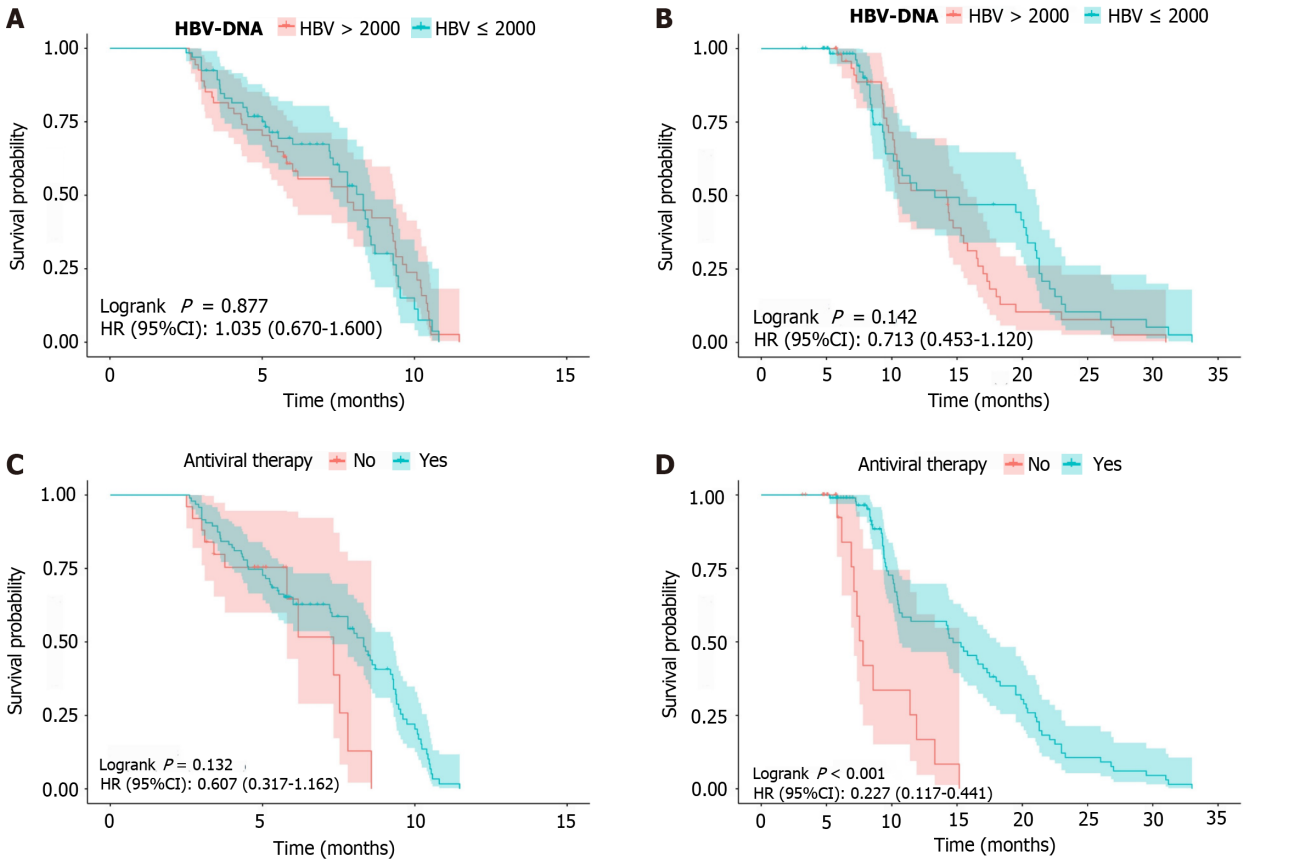

Figure 2 Graph showing the effect of different levels of hepatitis B virus-DNA on long-term survival of patients and further subgroup analysis according to antiviral treatment. A: Kaplan Meier plot of progression-free survival in the hepatitis B virus (HBV)-DNA ≤ 2000 and HBV-DNA > 2000 groups; B: Kaplan Meier plot of overall survival (OS) in the HBV-DNA ≤ 2000 and HBV-DNA > 2000 groups; C: Kaplan Meier plot of Analysis of progression-free survival subgroup by antiviral therapy; D: Kaplan Meier plot of Analysis of OS subgroup by antiviral therapy. HBV: Hepatitis B virus.

prediction models were constructed (Figure 3), yielding c-indexes of 0.65 (0.57–0.74) for the training set and 0.76 (0.66–0.85) for the validation set.

Validation of prognostic models

Patients were randomly assigned to the training dataset (*n* = 84) and internal validation dataset (*n* = 36) in a 7:3 ratio. The baseline characteristics of the training and validation datasets are shown in Table 6. The aera under the curves of the 9-month OS for the training set and internal validation set were 0.753 and 0.877 (Figure 4A and B), whereas those of the 12-

Table 4 Univariate and multivariate analyses of the prognostic factors for progression-free survival

Factors	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
AFP (≤ 1210 *vs* > 1210)	0.71 (0.46- 1.09)	0.121	-	-
Age (≥ 60 yr *vs* < 60 yr)	1.00 (0.65- 1.53)	0.984	-	-
Alcohol (Yes *vs* No)	0.93 (0.60- 1.45)	0.753	-	-
ALT (≤ 40 *vs* No)	0.81 (0.53- 1.24)	0.337	-	-
Antiviral therapy (Yes *vs* No)	0.61 (0.32- 1.16)	0.132	-	-
BCLC stage (C *vs* B)	0.55 (0.35 - 0.87)	0.011	0.57 (0.36-0.91)	0.017
BMI (Normal *vs* Low)	1.35 (0.61- 3.00)	0.457	-	-
BMI (Over obese *vs* Low)	0.46 (0.16- 1.31)	0.146	-	-
BMI (Weight *vs* Low)	0.87 (0.53- 1.44)	0.584	-	-
Child Pugh score (B *vs* C)	1.34 (0.86- 2.06)	0.192	-	-
Diabetes (Yes *vs* No)	1.02 (0.62 - 1.69)	0.929	-	-
Cirrhosis (Yes *vs* No)	0.99 (0.64- 1.52)	0.955	-	-
ECOG (2 *vs* 0-1)	1.92 (1.25- 2.96)	0.003	1.86 (1.21-2.86)	0.005
HBV (Positive *vs* Negative)	1.21 (0.76- 1.94)	0.417	-	-
HBV-DNA (HBV ≤ 2000 *vs* HBV > 2000)	1.04 (0.67- 1.60)	0.877	-	-
Hypertensive (Yes *vs* No)	0.97 (0.60- 1.56)	0.904	-	-
PVTT (Yes *vs* No)	1.36 (0.86- 2.13)	0.186	-	-
Post operative (Yes *vs* No)	0.78 (0.50- 1.22)	0.284	-	-
Metastasis (Yes *vs* No)	0.73 (0.47- 1.14)	0.164	-	-
Sex (male *vs* No)	0.83 (0.54- 1.28)	0.395	-	-
Smoking (Yes *vs* No)	0.95 (0.59- 1.53)	0.834	-	-
Total bilirubin (≤ 34 *vs* > 34)	0.92 (0.57- 1.48)	0.726	-	-
Virus reactivation (Yes *vs* No)	1.30 (0.18- 9.43)	0.798	-	-

HBV: Hepatitis B virus; BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer; PVTT: Portal vein tumor thrombosis.

month OS were 0.701 and 0.729 (Figure 4C and D), respectively. Subsequently, we plotted the calibration curves for the training set and validation set of 9- and 12-month OS (Figure 5). Using the calibration curves, we found that the model-predicted risk was more consistent with the actual occurrence of risk.

AEs

AEs were mainly reported by patients in both cohorts, featuring reactive proliferation of capillary endothelial cells in the skin, proteinuria, feelings of queasiness, low white blood cell count, elevated levels of bilirubin in the blood, and a reduced number of platelets. Importantly, none of the participants ceased treatment because of AEs, and there was no notable variation in the occurrence of AEs between the two groups ($P > 0.05$; Table 7).

DISCUSSION

This study represents the first comprehensive investigation into the treatment outcomes of patients with HCC receiving camrelizumab in combination with lenvatinib, alongside the development of a predictive model to assess their long-term prognosis. Our findings revealed no statistically significant differences in PFS, OS, ORR, and DCR between the two groups, aligning with prior studies[24,25]. Independent prognostic factors for PFS included BCLC classification and ECOG score, while AFP level, antiviral therapy, and portal vein cancer embolism emerged as independent prognostic factors for OS. Additionally, AEs were comparable between the two groups, with no deaths attributed to AEs.

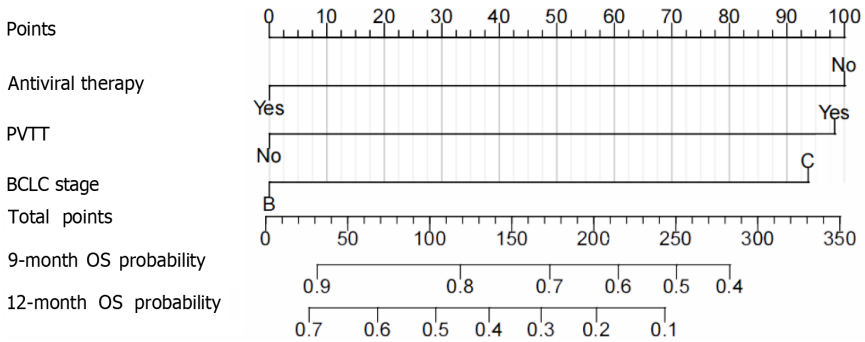

Figure 3 Graph showing the prognostic model for predicting 9- and 12-months overall survival. OS: Overall survival; PVTT: Portal vein tumour thrombus; BCLC: Barcelona Clinic Liver Cancer.

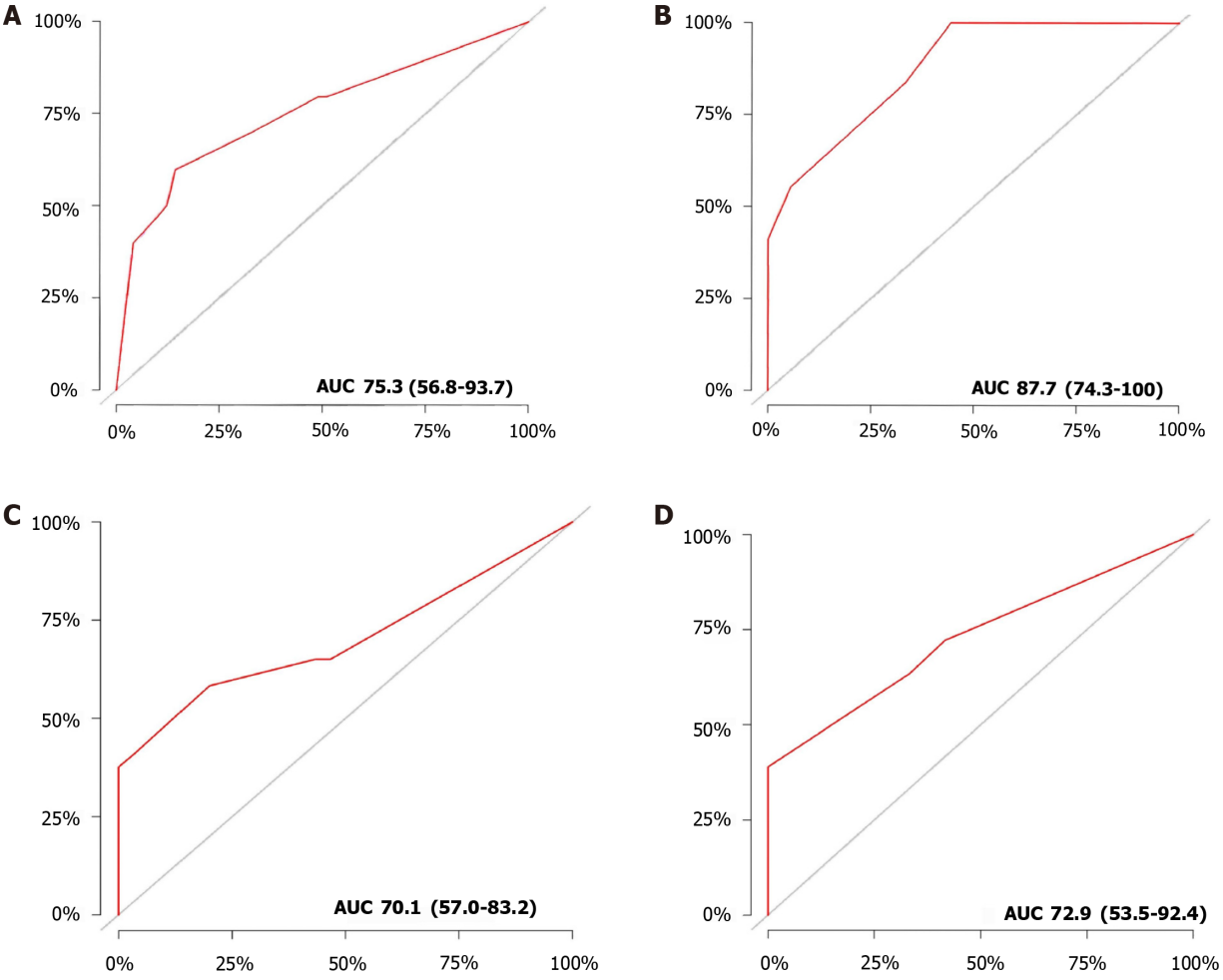

Figure 4 Graph showing the operating characteristic evaluation plot for prognostic model. A: Graph showing the training set receiver operating characteristic (ROC) evaluation plot for 9-month prognostic prediction model; B: Graph showing the validation set ROC evaluation plot for 9-month prognostic prediction model; C: Graph showing the training set ROC evaluation plot for 12-month prognostic prediction model; D: Graph showing the validation set ROC evaluation plot for 12-month prognostic prediction model. AUC: Aure under the curve.

Despite advancements in healthcare and living standards, chronic HBV infection remains a predominant etiological factor for HCC, particularly in regions like Asia and Africa, including China[26-28].

While some studies have suggested that HBV viral load may impact the efficacy of immune checkpoint inhibitors in certain malignancies like gastric and anal squamous carcinomas[15,29], the precise mechanisms remain unclear. It is hypothesized that HBV may interfere with the antitumor effects of immune checkpoint inhibitors within the tumor immune microenvironment. The integration of HBV into the genome of HCC cells and hepatocytes can induce an immune-mediated inflammatory response, further exacerbating hepatocellular DNA damage[30]. In the context of HCC, studies typically require a baseline HBV load of < 100 IU/mL for eligibility, yet the impact of baseline viral load on

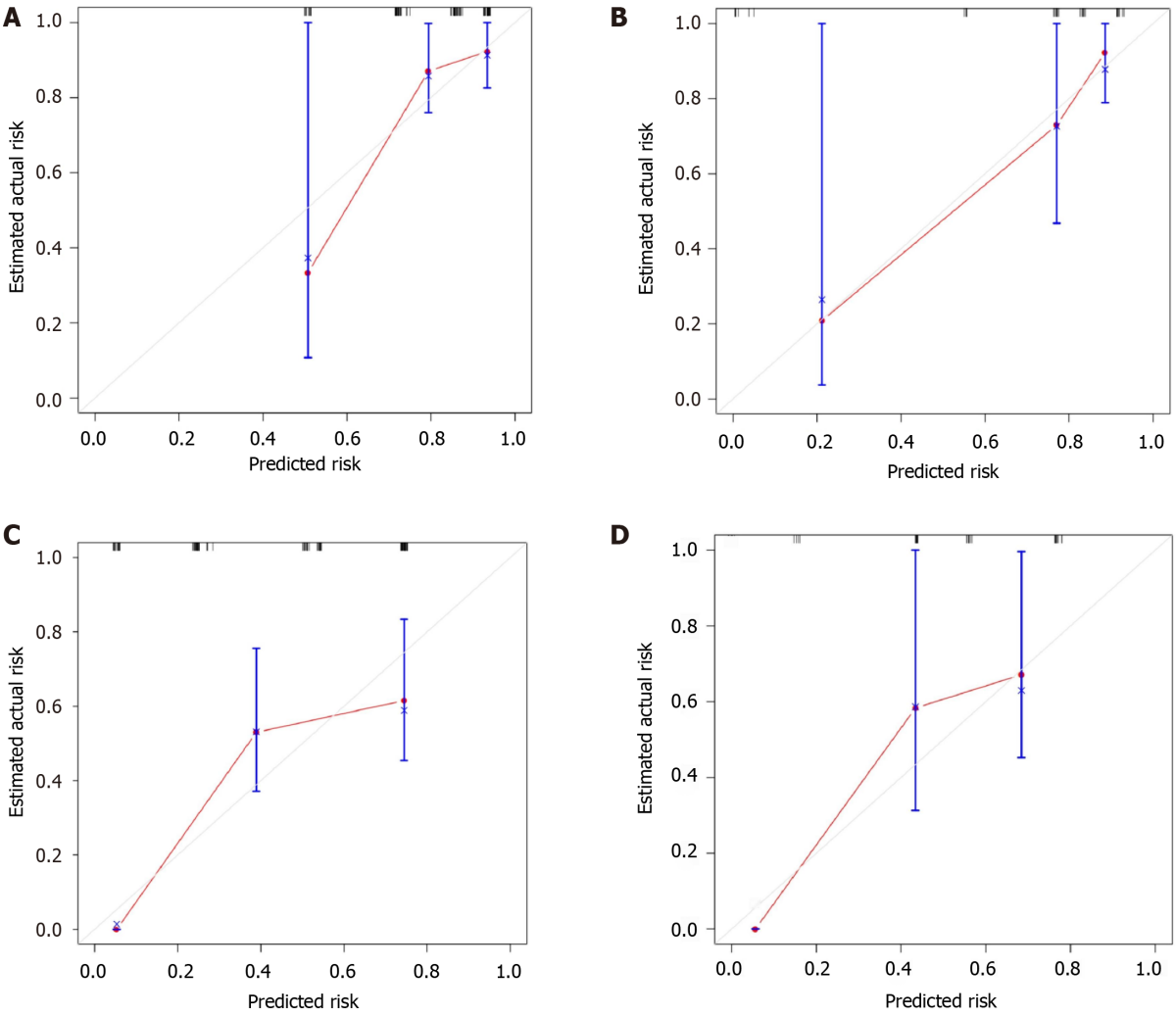

Figure 5 Graph showing the Calibration plots for prognostic model. A: Calibration plots for training set 9-months overall survival (OS); B: Calibration plots for validation set 9-months OS; C: Calibration plots for training set 12-months OS; D: Calibration plots for validation set 12-months OS.

clinical outcomes remains largely unexplored[31-33]. While IMbrave150 included a significant number of HBV-infected patients[11], it did not assess whether HBV load influenced the efficacy of the anti-PD-1 + antiangiogenic regimen or induced HBV reactivation. Significantly, Ho *et al*[34] discovered that the viral etiology did not affect the tumor immune microenvironment, indicating that viral status should not influence immune checkpoint inhibitor dosing. Consistent with our findings, it can be inferred that viral load does not significantly affect the efficacy of anti-PD-1 blockade.

Our research findings indicate that AFP level, antiviral treatment, and the presence of portal vein cancer thrombosis were identified as key independent factors influencing OS using multivariate Cox proportional hazard regression analyses. Subsequently, a prognostic nomogram incorporating these factors was developed. The diagram clearly illustrated that antiviral therapy had the most significant impact on OS, while portal vein cancer thrombosis had the least effect. Validation of the nomogram was performed by calculating the c-index and generating calibration curves. The validation c-index for the nomogram model was 0.76 (0.66-0.85), indicating good alignment with actual results and highlighting the reliability and accuracy of the model. External validation was not possible due to limited case availability. Additionally, the observed HBV reactivation rate in our study was consistent with that reported by Sun X *et al*[20] (1.6%).

In chronic HBV infection, HBV-specific CD8+ T cells have the ability to express PD-1 molecules[35]. By blocking the PD-1/PD-L1 binding, there is a partial restoration of their antiviral function. However, it is important to note that PD-1 also has a critical role in the prevention of severe liver injury. Consequently, interfering with the PD-1/PD-L1 axis could potentially result in hepatocyte destruction and the release of previously dormant virus into the bloodstream[36,37]. Furthermore, our study highlights that regardless of HBV-DNA levels, the prognosis of patients can be extended through antiviral therapy. Various research studies have demonstrated that antiviral therapy can increase the survival rates of individuals with HCC who are undergoing hepatectomy or sorafenib treatment[24,25]. To optimize outcomes, it is recommended to initiate antiviral therapy promptly in HBsAg-positive patients[38]. Sun *et al*[20] demonstrated that a case of HBV reactivation occurred despite undetectable baseline HBV DNA levels and no antiviral therapy during treatment. This finding suggests that HBsAg-positive patients receiving anti-PD-1 immunotherapy might benefit from antiviral treatment irrespective of their HBV-DNA levels. Although antiviral therapy can enhance the clinical prognosis for patients with HCC, the prognosis for those with advanced HCC continues to be poor.

Table 5 Univariate and multivariate analyses of the prognostic factors for overall survival

Factors	Univariate		Multivariate	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
AFP (≤ 1210 *vs* > 1210)	0.57 (0.36-0.92)	0.020	0.95 (0.56-1.60)	0.849
Age (≥ 60 yr *vs* < 60 yr)	0.89 (0.57-1.39)	0.618	-	-
Alcohol (Yes *vs* No)	0.93 (0.59-1.46)	0.750	-	-
ALT (≤ 40 *vs* No)	1.29 (0.83-2.02)	0.256	-	-
Antiviral therapy (Yes *vs* No)	0.23 (0.12-0.44)	<0.001	0.43 (0.20-0.89)	0.024
BCLC stage (C *vs* B)	2.44 (1.48-4.05)	0.001	2.22 (1.27-3.86)	0.005
BMI (Normal *vs* Low)	0.61 (0.26-1.45)	0.265	-	-
BMI (Over obese *vs* Low)	2.86 (1.00-8.21)	0.051	-	-
BMI over (Weight *vs* Low)	0.83 (0.51-1.37)	0.469	-	-
Child Pugh score (B *vs* C)	1.01 (0.65-1.59)	0.952	-	-
Diabetes (Yes *vs* No)	0.97 (0.57-1.66)	0.922	-	-
Cirrhosis (Yes *vs* No)	1.16 (0.74-1.83)	0.515	-	-
ECOG (2 *vs* 0-1)	0.98 (0.63-1.53)	0.937	-	-
HBV (Positive *vs* Negative)	1.03 (0.63-1.66)	0.914	-	-
HBV-DNA (HBV ≤ 2000 *vs* HBV > 2000)	0.71 (0.45-1.12)	0.142	-	-
Hypertensive (Yes *vs* No)	1.07 (0.65-1.76)	0.781	-	-
PVTT (Yes *vs* No)	2.64 (1.61-4.31)	< 0.001	2.28 (1.29-4.05)	0.005
Post operative (Yes *vs* No)	1.18 (0.75-1.88)	0.472	-	-
Metastasis (Yes *vs* No)	0.65 (0.41-1.04)	0.071	-	-
Sex (male *vs* No)	1.00 (0.64-1.56)	0.994	-	-
Smoking (Yes *vs* No)	1.25 (0.77-2.04)	0.374	-	-
Total bilirubin (≤ 34 *vs* > 34)	0.86 (0.53-1.39)	0.533	-	-
Virus reactivation (Yes *vs* No)	1.29 (0.18-9.35)	0.803	-	-

HBV: Hepatitis B virus; BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer; PVTT: Portal vein tumor thrombosis.

Nevertheless, our study has several limitations that need to be acknowledged. First, we limited the generalizability of our findings to other populations because the study was a retrospective single-center study, in which HBV is the prevalent cause of HCC in China. Second, in order to minimize the influence of varying treatment regimens on the results, we have only chosen one immunotherapy combination targeted therapy widely used in patients with advanced HCC in China (camrelizumab in combination with lenvatinib). Additionally, the exclusion of some patients from our study may have reduced its statistical power. Lastly, the sample size in our study was relatively small, which could potentially introduce bias into the result.

CONCLUSION

Our study demonstrates that level of HBV-DNA does not significantly affect prognosis and adverse effects in patients with HCC treated with camrelizumab and lenvatinib. However, the receipt of antiviral therapy emerged as the most significant predictor of long-term prognosis. Our study, based on non-randomized retrospective observational data, offers only limited evidence regarding the effectiveness and safety of these drugs. Therefore, these findings should not be solely relied upon for clinical decision-making without further evidence-based confirmation. To validate our results and provide more robust evidence for clinical practice in the future, prospective studies with longer follow-up periods and larger sample sizes are warranted.

Table 6 Comparison of training set and validation set features, *n* (%)

Characteristic	Training cohort, *n* = 84	Internal test cohort, *n* = 36	*P* value
HBV-DNA			0.749
> 2000	37 (44)	17 (47)	
≤ 2000	47 (56)	19 (53)	
HBV			0.001
Negative	67 (80)	18 (50)	
Positive	17 (20)	18 (50)	
Antiviral therapy			0.806
No	18 (21)	7 (19)	
Yes	66 (79)	29 (81)	
Child Pugh score			0.022
A	30 (36)	21 (58)	
B	54 (64)	15 (42)	
PVTT			0.780
No	42 (50)	19 (53)	
Yes	42 (50)	17 (47)	
BCLC stage			0.690
B	41 (49)	19 (53)	
C	43 (51)	17 (47)	
Metastasis			0.936
No	46 (55)	20 (56)	
Yes	38 (45)	16 (44)	
AFP			0.035
> 1210	48 (57)	13 (36)	
≤ 1210	36 (43)	23 (64)	
Sex			0.837
Female	31 (37)	14 (39)	
Male	53 (63)	22 (61)	
Age			0.968
< 60	44 (52)	19 (53)	
≥ 60	40 (48)	17 (47)	
BMI			0.333
Low	48 (57)	25 (69)	
Normal	5 (6.0)	3 (8.3)	
Obese	5 (6.0)	0 (0)	
Overweight	26 (31)	8 (22)	
ECOG			0.491
0-1	48 (57)	23 (64)	
2	36 (43)	13 (36)	
Post operative			0.569
No	49 (58)	23 (64)	
Yes	35 (42)	13 (36)	

ALT			0.262
> 40	35 (42)	19 (53)	
≤ 40	49 (58)	17 (47)	
Total bilirubin			0.049
> 34	62 (74)	20 (56)	
≤ 34	22 (26)	16 (44)	
Diabetes			0.066
No	59 (70)	31 (86)	
Yes	25 (30)	5 (14)	
Hypertensive			0.827
No	24 (29)	11 (31)	
Yes	60 (71)	25 (69)	
Cirrhosis			0.245
No	44 (52)	23 (64)	
Yes	40 (48)	13 (36)	
Smoking			0.365
No	56 (67)	27 (75)	
Yes	28 (33)	9 (25)	
Alcohol			0.228
No	51 (61)	26 (72)	
Yes	33 (39)	10 (28)	
Virus reactivation			0.512
No	83 (99)	35 (97)	
Yes	1 (1)	1 (3)	

Data in brackets represent the percentages of patients. HBV: Hepatitis B virus; BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; BCLC: Barcelona Clinic Liver Cancer; PVTT: Portal vein tumor thrombosis.

Table 7 Treatment-related adverse events in patients with hepatocellular carcinoma, *n* (%)

Variable	Group		*P* value
	HBV-DNA > 2000, *n* = 54	HBV-DNA ≤ 2000, *n* = 66	
Rash	4 (7)	6 (9)	> 0.999
Nausea	7 (13)	13 (20)	0.325
Diarrhea	5 (9)	5 (8)	0.752
Fatigue	4 (7)	6 (9)	> 0.999
Myocarditis	6 (11)	6 (9)	0.714
Hyperbilirubinemia	5 (9)	8 (12)	0.616
Hypertension	5 (9)	7 (11)	0.807
Leukopenia	6 (11)	8 (12)	0.864
Thrombocytopenia	7 (13)	10 (15)	0.732
RCCEP	23 (43)	31 (47)	0.632
Neutropenia	4 (7)	7 (11)	0.752
Proteinuria	14 (26)	18 (27)	0.868

Hypothyroidism	5 (9)	5 (8)	0.752
Elevated ALT	4 (7)	7 (11)	0.752
Elevated AST	7 (13)	6 (9)	0.497

Data in brackets represent the percentages of patients. HBV: Hepatitis B virus; RCCEP: Reactive cutaneous capillary endothelial proliferation; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

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FOOTNOTES

Author contributions: Qin XB and Han ZX designed the study; Pan D, Liu HN and Yao ZY collected the clinical data; Chen XX, Li YQ and Zhu JJ analyzed the data; Pan D, Liu HN and Yao ZY wrote the paper; Qin XB and Han ZX revised the paper; all authors contributed to the article and approved the submitted version. There are several reasons for designating Pan D and Liu HN as co-first authors, Qin XB and Han ZX as co-corresponding authors. Firstly, this study is a collaborative study, the setting of co-first authors and co-corresponding authors accurately reflects the distribution of responsibilities and burdens related to the time, effort required to complete the study and the final paper. This also ensures effective communication and management of post submission matters, ultimately improving the quality and reliability of the paper. Secondly, the completion of this study requires research design, conceptualization, and implementation (including data collection, data processing, and chart making), which require authors with different professional knowledge and skills. The designation of co-first authors and co-corresponding authors best reflects this diversity. Most importantly, Pan D and Liu HN made equally substantial efforts throughout the entire research process. Choose these researchers as co-first authors, acknowledge and respect this equal contribution, while recognizing the team spirit and collaborative spirit of this study. Qin XB and Han ZX developed detailed ideas for this study, reviewed the specific implementation process, supervised the overall quality and reliability of the paper. In summary, we believe that designating Pan D and Liu HN as co- first authors, Qin XB and Han ZX as co-corresponding authors, is suitable for our manuscript as it accurately reflects the collaborative spirit, equal contribution, and diversity of our team.

Institutional review board statement: The studies involving human participants were reviewed and approved by the Ethics Committee of Clinical Trials (Approval No. XYFY2022-KL207-01).

Informed consent statement: Due to the retrospective nature of this study, we waived the requirement for written informed consent.

Conflict-of-interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at qin_xiaobing@163.com.

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