Submitted: 28 December, 2025 Accepted: 17 April, 2026 Published: 30 August, 2026 DOI:10.22514/jomh.2026.069

ORIGINAL RESEARCH

JOMH Journal of Men's Health

Relationship between chronic hepatitis B virus infection and tumor progression in Chinese patients with advanced prostate cancer following combined androgen blockade therapy: a retrospective cohort study

Yu Wang[1], Huan Liao[2], Yi Liu[2], Zhili Cheng[2], Peng Guo[2,*]

[1]Department of Pathology, Neijiang First People's Hospital, 641000 Neijiang, Sichuan, China
[2]Department of Urology, Neijiang First People's Hospital, 641000 Neijiang, Sichuan, China

***Correspondence**
gp181759594@163.com
(Peng Guo)

Abstract

Background: The impact of chronic hepatitis B virus (HBV) infection on the progression of advanced prostate cancer (PCa) following combined androgen blockade (CAB) therapy remains uncertain. **Methods**: We retrospectively collected clinicopathological data and follow-up information from patients with advanced PCa who received CAB therapy at Neijiang First People's Hospital (Neijiang, China) between January 2010 and December 2023. Based on the baseline hepatitis B surface antigen (HBsAg) status, the patients were categorized into HBsAg-negative and HBsAg-positive groups, and the clinical characteristics between the two groups were compared. The Kaplan-Meier (K-M) survival curve and models of multivariate Cox regression were used to assess the association between chronic HBV infection and prognosis after CAB. **Results**: A total of 385 patients were included in this study, among whom 28 were HBsAg-positive (7.27%). Of these, 26 (92.9%) were inactive HBsAg carriers, and the remaining 2 (7.1%) had active chronic hepatitis B. The mean age in the HBsAg-positive group was significantly lower than that in the HBsAg-negative group (66.6 $\pm$ 5.3 years *vs.* 75.9 $\pm$ 7.0 years, $p < 0.001$). K-M survival analysis demonstrated that HBsAg-positive patients progressed to the castration-resistant stage more rapidly (median time: 19 *vs.* 40 months, Log-rank $\chi^2 = 15.895$; $p < 0.001$). Multivariate Cox regression further revealed that HBsAg-positive patients had a 2.15-fold increased risk of progression to castration-resistant prostate cancer (CRPC) compared to HBsAg-negative patients (95% confidence interval (CI): 1.15–4.04, $p = 0.017$). Subgroup analyses demonstrated no statistically significant interactions (all $p > 0.05$). **Conclusions**: Chronic HBV infection is associated with an earlier onset of PCa and a shorter time to progression to CRPC in patients with advanced PCa after CAB therapy.

Keywords

Prostate cancer; Hepatitis B virus; Combined androgen blockade; Castration-resistant prostate cancer

1. Introduction

The incidence rate of prostate cancer (PCa) in China is increasing in all age groups, and the mortality has increased since 2005 [1]. Compared to developed Western countries, China has a higher proportion of patients newly diagnosed with advanced PCa, including locally advanced cases or those with distant metastases. Consequently, many of these patients are only able to receive endocrine therapy. Studies have demonstrated that combined androgen blockade (CAB)—a treatment approach that pairs surgical or medical castration with antiandrogen medication yields better outcomes in terms of both progression-free survival (PFS) and overall survival (OS) when compared to standalone androgen deprivation therapy (ADT) [2]. According to the current guidelines, for patients with advanced PCa, ADT in combination with either docetaxel or novel androgen receptor axis-targeting (ARAT) agents is recommended as the standard first-line therapeutic option [3, 4]. However, in the vast western regions of China, the initial treatment regimen for most patients with advanced PCa still consists of ADT combined with bicalutamide, primarily due to three key factors: first, a significant proportion of the population has relatively low incomes, and the medical insurance system remains inadequate [5]; second, Asian individuals demonstrate increased sensitivity to ADT compared to their white counterparts [6]; and third, the frequency of *HSD3B1* gene mutations (encoding 3β-hydroxysteroid dehydrogenase 1, which is associated with ADT resistance) is

significantly lower in the Asian population (8.7%–17.5%) than in the American population (47.9%–52.9%) [7–11]. Even with CAB treatment, most patients will inevitably progress to the castration-resistant stage, at which point there are few effective available treatment options, leading to poor efficacy and prognosis.

The etiology of PCa remains unclear. Reports indicate that human viral infections can promote cancer development [12]. Research has indicated that several viruses, including various subtypes of human papillomaviruses (HPVs), Epstein-Barr virus (EBV), BK virus (BKV), and human cytomegalovirus (HCMV), are linked to the onset of prostate cancer (PCa) [12, 13]. However, the relationship between hepatitis B virus (HBV) infection and PCa is still poorly studied, and conclusions remain inconsistent. A recent study led by Ishiguro *et al.* [14], which analyzed 30 non-cancerous prostate tissue samples alongside 182 PCa specimens, concluded that HBV infection does not correlate with the development of PCa. In contrast, Sarka *et al.* [15] detected HBV-DNA in PCa tissues and demonstrated a significant correlation between HBV infection and PCa. The overall incidence rate of HBV infection in mainland China is approximately 6.89%, which suggests that approximately 84 million people were living with hepatitis B virus surface antigen (HBsAg) in 2018 [16]. The World Health Organization (WHO) states that between 20% and 30% of adults living with chronic HBV infection go on to develop cirrhosis and/or liver cancer. Although HBV is a hepatotropic virus, it can also be detected in extra-hepatic tissues such as the kidney [17], prostate [15], nasopharynx [18], and pancreas [19]. Some extra-hepatic cancers are associated with HBV infection, and the mean age at cancer diagnosis was younger in HBV-infected patients compared to those without the infection [19–21]. Additionally, Huang *et al.* [18] reported that nasopharyngeal carcinoma (NPC) in HBsAg-positive patients is associated with higher rates of distant metastasis and poorer overall survival compared to HBsAg-negative cases.

HBV infection remains a major public health challenge in China. Regionally, the incidence was highest in Western China (8.92%) compared to central (5.23%) and eastern (6.61%) regions [16]. In economically underdeveloped western areas, patients often have lower health examination awareness, leading to delayed diagnosis of PCa. Consequently, many present with advanced disease and are limited to CAB therapy. Notably, the clinical and pathological features, treatment response, and time to castration-resistant prostate cancer (CRPC) progression in HBsAg-positive advanced PCa patients, compared to their HBsAg-negative counterparts, remain unreported. This study aims to fill this critical knowledge gap.

2. Materials and methods

2.1 Inclusion criteria

The inclusion criteria were as follows: (1) Patients diagnosed with advanced prostatic adenocarcinoma (locally advanced and/or distant metastases) confirmed by prostate needle biopsy, magnetic resonance imaging (MRI) of the pelvis, and computed tomography (CT) scans of the abdomen and chest, and radionuclide bone scan at the First People's Hospital of Neijiang (Neijiang, China) between 01 January 2010, and 31 December 2023; (2) Patients with PCa received ADT using one of the following regimens: subcutaneous injection of leuprorelin (3.75 mg) every 4 weeks, or subcutaneous injection of goserelin (3.6 mg) every 4 weeks, or bilateral orchiectomy, or subcutaneous injection of goserelin (10.8 mg) every 12 weeks, and all regimens were administered in combination with oral bicalutamide (50 mg daily); and (3) Patients who underwent regular follow-up: after initiating CAB therapy, prostate-specific antigen (PSA) levels were measured monthly during the first three months. Subsequently, the follow-up interval for PSA testing was adjusted based on PSA trends: testing was performed every 3 months if levels demonstrated a stable decline, or every 2–4 weeks if an upward trend was detected. Imaging studies were scheduled according to PSA levels and the presence of symptoms (*e.g.*, new-onset bone pain or recurrent urinary obstruction). Serum testosterone levels were measured every 3–6 months.

2.2 Exclusion criteria

The following were defined as exclusion criteria: (1) Patients lacking complete personal information; (2) Patients diagnosed with other forms of malignant tumors; (3) Patients who underwent prostatectomy after CAB treatment; (4) Patients who received other treatments (*e.g.*, chemotherapy, radiotherapy, immunotherapy, or targeted therapy) prior to progression to CRPC; (5) Patients with viral hepatitis other than hepatitis B.

2.3 Data collection

The follow-up period was set to conclude on 01 March 2025. Based on previous literature reports [22, 23] and clinical experience, we collected the following baseline characteristics and clinical data: age; hemoglobin (Hb); initial PSA; body mass index (BMI); alanine aminotransferase (ALT); albumin; tumor-node-metastasis (TNM) clinical stage; Gleason score; bone metastasis status; smoking and drinking history; diabetes mellitus (DM); hypertension; HBsAg status; PSA nadir (nPSA) and time to PSA nadir (TTN). Additionally, the results of the hepatitis B serological panel test conducted after at least six months of CAB treatment were also collected for patients who were positive for HBsAg at baseline. For patients ultimately included in the analysis, stratification was performed based on their baseline HBsAg status, dividing them into the HBsAg-negative group and the HBsAg-positive group. HBV infection was defined by a positive HBsAg test. Patients were categorized as drinkers or smokers if they had a history of alcohol consumption or tobacco use within one year prior to their PCa diagnosis.

2.4 Endpoint selection rationale

The primary endpoint of this study was the diagnosis of CRPC, as defined by the 2016 European Association of Urology (EAU) guideline [24]. CRPC was selected as the endpoint, rather than overall survival (OS), for two reasons: (1) prior studies have demonstrated that the time from diagnosis to CRPC is a significant prognosticator of OS and thus serves as a valid surrogate endpoint [25]; (2) additionally, due to the high

cost of novel ARAT and concerns about chemotherapy-related toxicities, many patients in this region did not receive effective treatment after progression to CRPC, leading to a significant increase in patients lost to follow-up.

2.5 Statistical analysis

Statistical analysis was conducted using R version 4.2.1 (http://www.Rproject.org; The R Foundation, Vienna, Austria) and the Free Statistics software (version 2.0; Beijing Free Clinical Medical Technology Co., Ltd, Beijing, China). In this study, quantitative data were analyzed using either the mean ± standard deviation (SD) or the median and interquartile range (IQR), depending on the data type. Qualitative variables were expressed as proportions (%). For quantitative data exhibiting a normal distribution and homogeneous variance, the Student's *t*-test was applied. The Mann-Whitney U test was utilized for quantitative data that did not conform to a normal distribution. Chi-square tests were employed to analyze categorical data.

Time to CRPC development in the two groups was estimated using the Kaplan-Meier survival curves, and the differences were determined using the log-rank test. The association between HBV infection and PCa progression after CAB was analyzed using Cox regression models. Both non-adjusted and multivariate adjusted models were used. Subgroup analyses were conducted to investigate the stability of the association between HBV infection and progression of advanced PCa after CAB treatment. Statistical significance was assessed by comparing adjusted hazard ratios (HRs) with 1.0 and describing 95% confidence intervals (CIs). In all tests, a *p*-value less than 0.05 was considered statistically significant.

3. Results

3.1 Patient enrollment and HBV status characterization

The detailed exclusion process is shown in Fig. 1. Ultimately, a total of 385 patients were included in this study, including 28

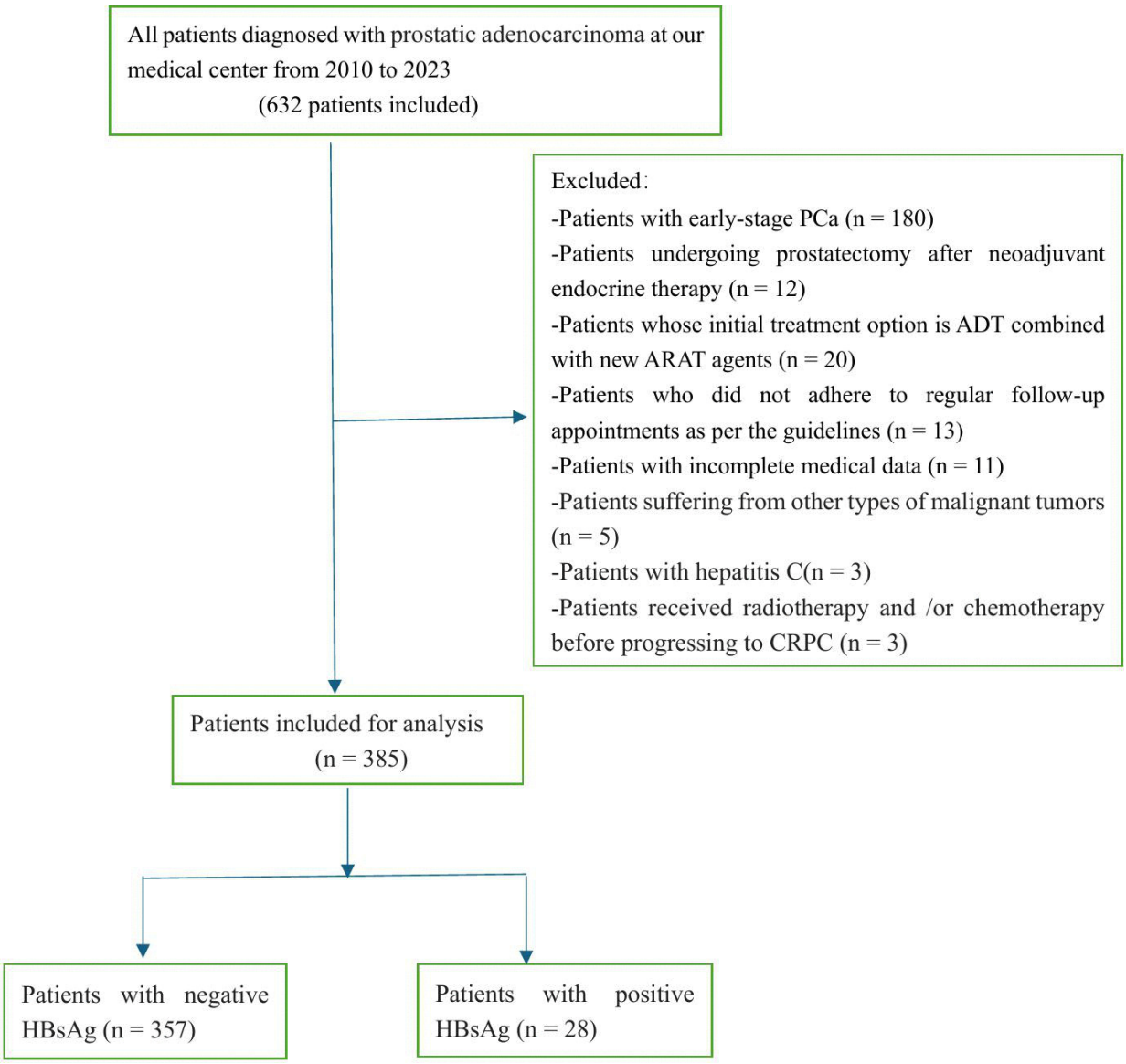

FIGURE 1. Flow diagram of this study. PCa: prostate cancer; ADT: androgen deprivation therapy; ARAT: androgen receptor axis-targeting; CRPC: castration-resistant prostate cancer; HBsAg: hepatitis B virus surface antigen.

HBsAg-positive patients (7.27%). All 28 HBsAg-positive patients tested positive for hepatitis B core antibody (HBcAb) and negative for hepatitis B surface antibody (HBsAb). The study follow-up concluded on 01 March 2025, with a median follow-up duration of 36.3 months. Prior to the diagnosis of PCa, 75% (21/28) of patients were unaware of their HBV infection, and none of them had received oral antiviral therapy for hepatitis B. Among these 28 patients, 26 were inactive HBsAg carriers (characterized by ALT levels below 30 U/L and HBV-DNA levels not exceeding 2000 IU/mL); the remaining 2 had active chronic hepatitis B (characterized by ALT levels exceeding 30 U/L and HBV-DNA levels greater than 2000 IU/mL). Notably, color doppler ultrasound examination revealed that none of the patients had liver cirrhosis.

3.2 HBV management and follow-up outcomes

After the diagnosis of PCa, the two patients with chronic hepatitis B in the active phase received entecavir treatment; both achieved undetectable HBV-DNA levels within 6 months. None of the patients with positive HBsAg at baseline underwent liver biopsy owing a lack of clinical indications. All patients in Group 2 received regular follow-up examinations for hepatitis B serological markers. During the follow-up period, conducted every six months to one year, none of the patients experienced HBsAg seroconversion to negative.

3.3 Comparative demographics and treatment responses between groups

The demographic details of the two groups are presented in Table 1. The mean age in the HBsAg-positive group was significantly lower than that in the HBsAg-negative group (66.6 $\pm$ 5.3 years *vs.* 75.9 $\pm$ 7.0 years, $p < 0.001$). After CAB treatment, patients in the HBsAg-positive group exhibited higher nadir PSA levels ($p = 0.021$) and a shorter time to nadir PSA (10.5 months *vs.* 17.0 months, $p = 0.001$).

3.4 CRPC progression and PFI comparison by HBsAg status

As of the follow-up cutoff date, a total of 168 (43.6%) patients who underwent CAB had demonstrated progression to CRPC. The Kaplan-Meier survival curves of the two groups are plotted in Fig. 2. The estimated median time to CRPC, development based on the Kaplan-Meier survival analysis was 40 (95% CI, 38.0–41.9) months in the HBsAg-negative group and 19 (95% CI, 4.6–33.4) months in the HBsAg-positive group. Comparison by log-rank test showed that the progression-free interval (PFI) was significantly shorter in the HBsAg-positive group than in the HBsAg-negative group ($\chi^2 = 15.895$; $p < 0.001$).

3.5 Univariate analysis

Based on univariate Cox regression analysis (Table 2), Hb, bone metastasis, age, Gleason score, albumin, initial PSA, nPSA, TTN, and HBV infection were all significantly associated with progression to CRPC (all $p < 0.05$). The collinearity assessment revealed that no collinearity existed among the specified independent variables.

3.6 Multivariate analysis

The findings from the multivariate Cox regression analysis are shown in Table 3. In each of the models (model I to Model IV), HBV infection demonstrated an association with an elevated risk of progression to CRPC. The corresponding HRs and 95% CIs were 2.75 (1.64–4.63), 2.93 (1.66–5.15), 2.1 (1.14–3.85), and 2.15 (1.15–4.04), respectively.

3.7 Subgroup analysis

In the subgroup analysis stratified by age, TNM stage, Gleason score, bone metastasis status, diabetes mellitus, and hypertension, the association between HBV infection and CRPC progression risk was explored in Fig. 3. No significant interactions were detected among the subgroups (All interaction *p*-values exceeded 0.05).

3.8 Time-dependent ROC

As illustrated in Fig. 4, a time-dependent receiver operating characteristic (ROC) curve was generated. A thorough examination of this curve demonstrated that during the initial stage after the commencement of CAB therapy (for example, at $t = 8$ months), the HBV infection status demonstrated good discriminatory ability in predicting the progression of CRPC, as evidenced by an area under the curve (AUC) value of 0.71. However, as time progresses (such as at $t = 28$ months), the predictive efficacy of HBV infection status for CRPC progression declined substantially, with the AUC value decreasing to 0.55.

4. Discussion

Lu *et al.* [21] examined 10 common extra-hepatic cancers among 60,323 adolescents and young adults up to 20 years old and found that the mean age at cancer diagnosis was 1.5–5.5 years younger in patients with HBsAg-positive compared to patients with HBsAg-negative. This finding was further confirmed as the mean age at diagnosis was 9.3 years younger (66.6 years *vs.* 75.9 years, $p < 0.001$) in patients with HBsAg-positive compared to those with HBsAg-negative. Compared to the prevalence rate (8.92%) of HBV infection in western China, only 7.27% of the patients in this study were HBsAg-positive. These findings appear to suggest that HBV infection does not increase the incidence of PCa, but for patients who carry susceptibility genes for PCa or possess carcinogenic risk factors, it is more likely to develop PCa at an early stage.

In this study, we also found that although the Gleason score of HBsAg-positive patients was not significantly higher than that of HBsAg-negative patients, HBsAg-positive patients progressed to CRPC within a shorter period of time. This finding suggests that HBV infection promotes PCa progression after CAB treatment, although the underlying mechanism remains unclear. The mechanism of CRPC is complex and is currently believed to involve both androgen receptor (AR)-dependent and AR-independent signaling pathways.

The HBV X protein (HBx), encoded by the HBV X gene, is

TABLE 1. Baseline characteristics of participants.

Variables	Total (n = 385)	HN group (n = 357)	HP group (n = 28)	*p*
Hb (g/L), Mean ± SD	127.6 ± 14.7	127.4 ± 14.6	130.3 ± 15.6	0.312
Bone metastasis, n (%)				
No	189 (49.1)	176 (49.3)	13 (46.4)	0.770
Yes	196 (50.9)	181 (50.7)	15 (53.6)	
Age (yr), Mean ± SD	75.2 ± 7.3	75.9 ± 7.0	66.6 ± 5.3	<0.001
Gleason score, n (%)				
7	74 (19.2)	71 (19.9)	3 (10.7)	0.434
8	151 (39.2)	136 (38.1)	15 (53.6)	
9	141 (36.6)	132 (37.0)	9 (32.1)	
10	19 (4.9)	18 (5.0)	1 (3.6)	
TNM stage, n (%)				
2	7 (1.8)	7 (2.0)	0 (0.0)	0.287
3	220 (57.1)	200 (56.0)	20 (71.4)	
4	158 (41.0)	150 (42.0)	8 (28.6)	
Hypertension, n (%)				
No	287 (74.5)	267 (74.8)	20 (71.4)	0.694
Yes	98 (25.5)	90 (25.2)	8 (28.6)	
Smoking, n (%)				
No	260 (67.5)	241 (67.5)	19 (67.9)	0.970
Yes	125 (32.5)	116 (32.5)	9 (32.1)	
Drinking, n (%)				
No	300 (77.9)	280 (78.4)	20 (71.4)	0.390
Yes	85 (22.1)	77 (21.6)	8 (28.6)	
Diabetes, n (%)				
No	326 (84.7)	303 (84.9)	23 (82.1)	0.784
Yes	59 (15.3)	54 (15.1)	5 (17.9)	
BMI ($kg \cdot m^{-2}$), Mean ± SD	22.6 ± 1.5	22.6 ± 1.5	22.8 ± 1.3	0.326
Albumin (g/L), Mean ± SD	40.0 ± 3.0	40.1 ± 3.0	39.7 ± 2.8	0.524
Initial PSA, n (%)				
<50 ng/mL	141 (36.6)	133 (37.3)	8 (28.6)	0.054
50–100 ng/mL	104 (27.0)	91 (25.5)	13 (46.4)	
>100 ng/mL	140 (36.4)	133 (37.3)	7 (25.0)	
TTN (mon), Median (IQR)	17.0 (12.0, 24.0)	17.0 (12.0, 24.0)	10.5 (6.8, 20.0)	0.001
ALT (U/L), Median (IQR)	15.0 (12.0, 22.0)	15.0 (12.0, 22.0)	16.0 (11.8, 21.0)	0.872
HBV-DNA (IU/mL)				
≤2000			26 (92.9)	
>2000			2 (7.1)	
nPSA (ng/mL), Median (IQR)	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)	0.1 (0.0, 3.6)	0.021

ALT: alanine aminotransferase; BMI: body mass index; Hb: Hemoglobin; HN group: HBsAg-negative group; HP group: HBsAg-positive group; nPSA: PSA nadir; PSA: prostate-specific antigen; SD: standard deviation; TTN: time to PSA nadir; HBV: hepatitis B virus; TNM: tumor-node-metastasis; IQR: interquartile range.

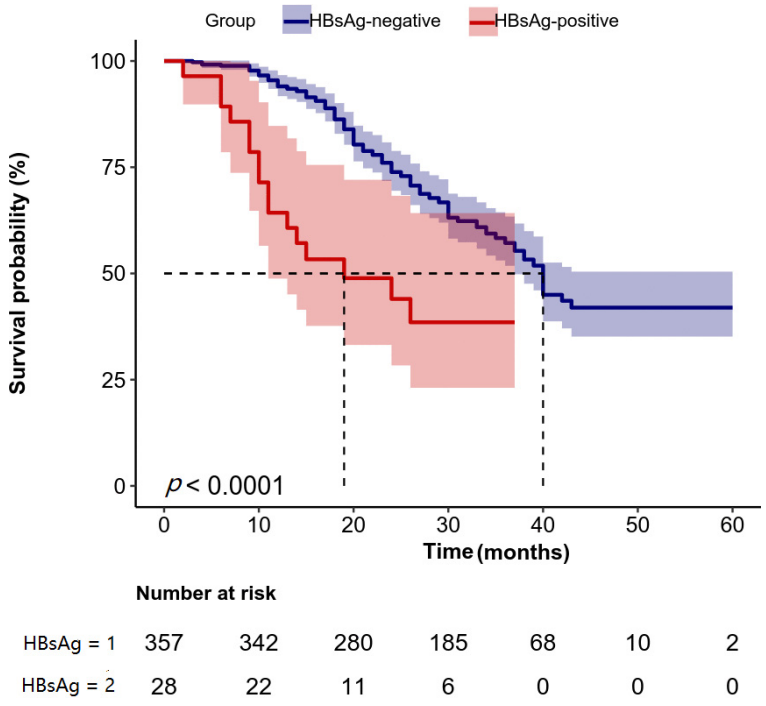

FIGURE 2. K-M survival curves of the two groups after receiving CAB therapy. The endpoint of this study was the diagnosis of CRPC; HBsAg = 1: HBsAg-negative group; HBsAg = 2: HBsAg-positive group. HBsAg: hepatitis B virus surface antigen.

TABLE 2. Association of covariates and CRPC progression risk.

Item	HR (95% CI)	*p* (Wald's test)
Hb (cont. var.)	0.99 (0.98, 1.00)	0.023
Bone metastasis: yes *vs.* no	1.70 (1.25, 2.31)	<0.001
Age (cont. var.)	0.97 (0.95, 0.99)	0.009
Gleason score: ref. = 7		
8	3.00 (1.67, 5.38)	<0.001
9	7.16 (4.02, 12.74)	<0.001
10	10.33 (4.51, 23.69)	<0.001
TNM stage: ref. = 2		
3	2.74 (0.38, 19.64)	0.317
4	3.59 (0.50, 25.85)	0.204
Hypertension: yes *vs.* no	1.29 (0.91, 1.81)	0.148
Smoking: yes *vs.* no	1.06 (0.77, 1.45)	0.728
Drinking: yes *vs.* no	1.11 (0.77, 1.59)	0.573
Diabetes: yes *vs.* no	1.02 (0.67, 1.56)	0.922
BMI (cont. var.)	0.94 (0.85, 1.04)	0.208
ALT (cont. var.)	1.01 (0.99, 1.03)	0.201
Albumin (cont. var.)	0.93 (0.89, 0.98)	0.005
Initial PSA: ref. = 1		
2	2.26 (1.53, 3.34)	<0.001
3	1.81 (1.24, 2.63)	0.002
nPSA (cont. var.)	1.32 (1.25, 1.38)	<0.001
TTN (cont. var.)	0.82 (0.80, 0.84)	<0.001
HBsAg: yes *vs.* no	2.75 (1.64, 4.63)	<0.001

HR: hazard ratio; CI: confidence interval; Hb: hemoglobin; ALT: alanine aminotransferase; BMI: body mass index; nPSA: PSA nadir; PSA: prostate-specific antigen; TTN: time to PSA nadir; HBsAg: hepatitis B virus surface antigen; cont: continuous; var: variable; ref: reference; TNM: tumor-node-metastasis.

TABLE 3. HBV infection and CRPC progression risk: multivariate analysis.

Variable	n (total)	n (event (%))	Model I HR (95% CI)	*p*	Model II HR (95% CI)	*p*	Model III HR (95% CI)	*p*	Model IV HR (95% CI)	*p*
HBsAg (−)	357	152 (42.6)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
HBsAg (+)	28	16 (57.1)	2.75 (1.64–4.63)	<0.001	2.93 (1.66–5.15)	<0.001	2.1 (1.14–3.85)	0.017	2.15 (1.15–4.04)	0.017

Model I: unadjusted.
Model II: adjusted for Gleason score + nPSA + TTN + initial PSA + bone metastasis.
Model III: Model II + albumin + age + Hb.
Model IV: Model III + TNM stage + ALT + BMI + hypertension + diabetes + smoking + drinking.
HR: hazard ratio; CI: confidence interval; HBsAg: hepatitis B virus surface antigen; Ref: reference.

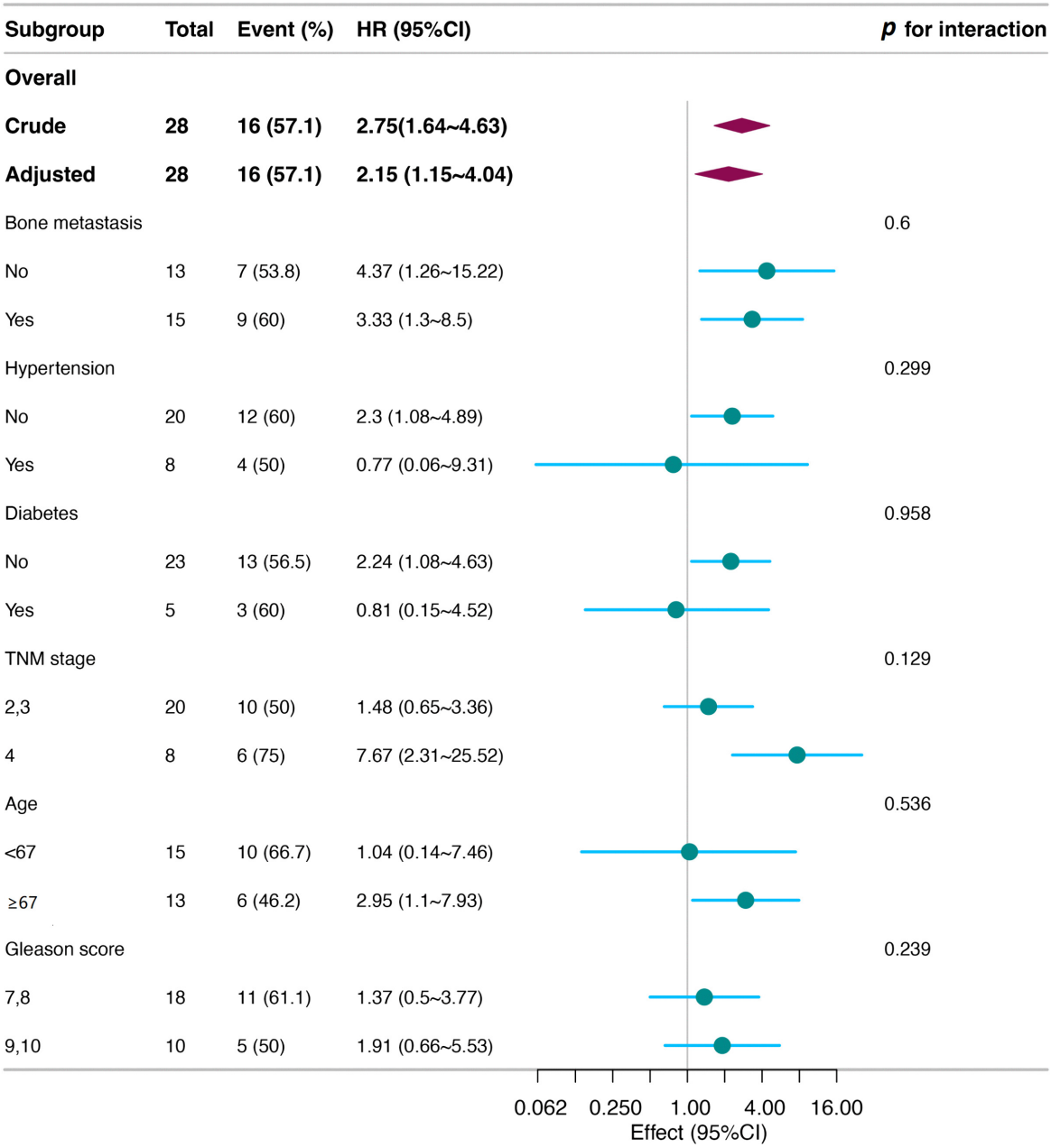

FIGURE 3. Subgroup analysis of HBV-CRPC risk association. Each stratification was adjusted for all factors except the stratification factor itself. HR: hazard ratio; CI: confidence interval; TNM: tumor-node-metastasis.

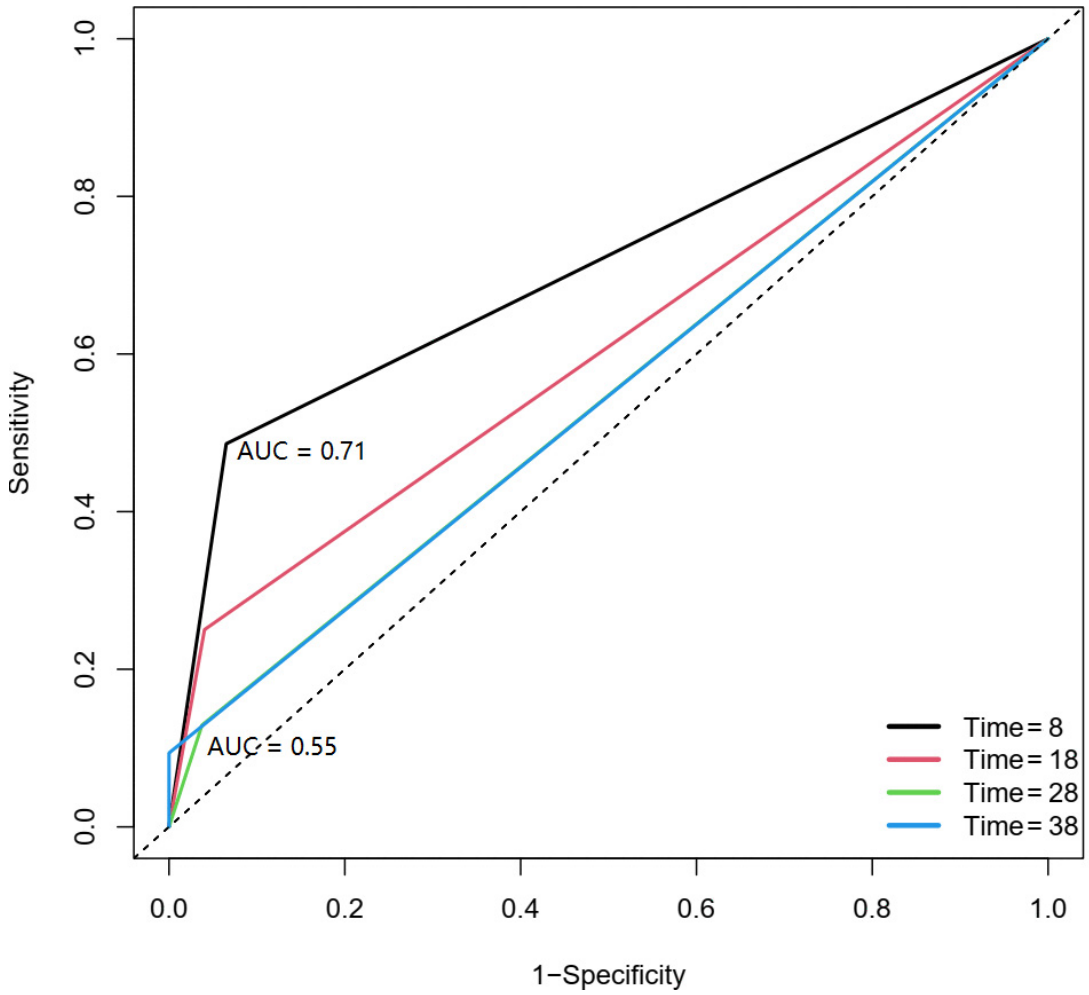

FIGURE 4. Time-dependent ROC: HBV's predictive efficacy change on CRPC. AUC: area under the curve.

known to activate signal transduction pathways and influence gene transcription in liver cells, which has been implicated in HBV-associated carcinogenesis [26]. Since HBV-DNA has been detected in some PCa tissues [15], we speculate that HBx may also exist in PCa cells and prostate cancer stem cells (PCSCs), where it may play an important role after endocrine therapy, leading to early progression to the castration-resistant stage. We further speculate that HBx in PCa tissues may contribute to both androgen receptor (AR)-dependent and AR-independent signaling pathways.

4.1 The AR-dependent signaling pathway

The AR-dependent signaling involves the following mechanisms: amplification and overexpression of the AR gene, AR gene mutations, alterations in androgen biosynthesis, as well as the involvement of AR co-activators and expression of AR splice variants (AR-Vs). Zhu *et al.* [27] found that HBx was correlated with elevated AR expression in hepatocellular carcinoma (HCC) and induced AR expression by stimulating its transcription in liver cell lines. Based on this finding, we hypothesize that HBx in PCa tissues may influence the stability and activity of AR in PCa cells through the following signaling pathways:

1. It is plausible that HBx enhances AR stability and activity directly. This effect may occur by increased AR phosphorylation mediated by HBx-induced activation of the cellular Src (c-Src) kinase signaling pathway. Notably, HBx does not physically associate with ligand-bound AR in the nucleus [28].

2. It has been reported that augmented mitogen-activated protein kinase (MAPK) signaling, which is required for both ligand-dependent and ligand-independent activation of AR, is correlated with castration-resistance and metastatic progression [29]. HBx can transactivate the MAPK signaling pathway in association with the mobilization of cytosolic Ca^{2+}, and the activated MAPK further activates AR [30].

3. In human PCa cells, AR can be activated by interleukin-6 (IL-6) even in the absence of androgens [31]. It has been found that serum levels of IL-6 are significantly higher in patients with acute and chronic hepatitis B compared to those in healthy individuals [32]. Elevated IL-6 concentrations may promote the occurrence of CRPC through multiple pathways: activation of the MAPK signaling pathway leading to AR activation [31]; overexpression of IL-6 increases PCa cell resistance to bicalutamide via transcriptional intermediary factor 2 (TIF2) [33]; and it can also directly activate the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway to enhance AR stability and activity [34].

4. Seo *et al.* [35] reported that in the absence of androgens, the Wnt/β-catenin pathway can activate AR-mediated transcription by up-regulating the Hippo pathway effector

Yes-associated protein (YAP). Furthermore, the Wnt/β-catenin pathway crosstalks with the androgen pathway, so β-catenin signaling therefore confers resistance to androgen inhibitors [36]. Many studies have shown that HBx can activate the Wnt/β-catenin signaling pathway and promote β-catenin accumulation through multiple pathways [37].

5. Glioma-associated oncogene homolog 2 (GLI2), a transcription factor in the Hedgehog (Hh) pathway, can potentially serve as a co-activator of AR [38]. Overexpression of GLI2 in lymph node carcinoma of the prostate (LNCaP) cells enhanced AR-specific gene expression in the absence of androgen [38]. Li *et al.* [39] also found that GLI2 may function by supporting the androgen signaling pathway in CRPC cells through the co-activation of full-length AR and its splice variants. HBx has been found to upregulate the level of GLI2 mRNA and increase the stability of GLI2 in liver cancer cells [40].

4.2 The AR-independent signaling pathway

AR-independent signaling pathways encompass several key mechanisms, including epithelial-mesenchymal transition (EMT), inactivation of the phosphatase and tensin homolog (*PTEN*) gene, activation of the PI3K/AKT signaling pathway, activation of the Wnt/β-catenin pathway, as well as the production and self-renewal of PCSCs [41].

1. EMT contributes to the development of CRPC through two distinct pathways: the Yes-associated protein 1 (YAP1) pathway, where YAP1, a crucial protein within the Hippo pathway, plays a significant role in promoting the transcriptional regulation of EMT and may induce the emergence of cancer stem cells (CSCs) [42], with studies reporting that overexpression of YAP1 can drive cell proliferation, castration-resistant growth, invasion, and enhance the metastatic potential of PCa cells [43], notably, HBx has been shown to upregulate YAP1 expression in liver cancer cells to facilitate their growth [44], and moreover, Huang *et al.* [18] discovered that in HBsAg-positive NPC samples, HBx could upregulate YAP1 expression to further promote cell invasiveness and metastasis via EMT; and the signal transducer and activator of transcription 3 (STAT3) pathway, in which STAT3 can be activated through multiple signaling cascades, with sustained activation of STAT3 in PCa cells inducing EMT and thus increasing their metastatic and invasive capabilities [45], Liu *et al.* [46] demonstrated that persistent activation of STAT3 in PCa cells leads to the development of CRPC while downregulation of STAT3 expression restores the sensitivity of PCa cells to chemotherapy. In liver cells, HBx can activate STAT3 and subsequently promote EMT [47].

2. The PI3K/AKT pathway is negatively regulated by the PTEN tumor suppressor [48], and loss of PTEN or activation of the PI3K/AKT pathway results in enhanced cell proliferation, survival, migration, and castration-resistant growth in PCa [49]. HBx is thought to lead to PTEN inactivation and activation of the PI3K/AKT pathway through the following mechanisms: Firstly, HBx directly interacts with mitochondrial membrane proteins, which may then increase the levels of mitochondrial reactive oxygen species (ROS) and lipid peroxide production [50]; by promoting the oxidation of cysteine residues within PTEN, the ROS induced by HBx can inactivate PTEN and enhance the function of AKT [51]. Secondly, HBx may cause an increase in IL-6 concentration, and elevated IL-6 levels could further activate the PI3K/AKT pathway [34].

3. PCSCs, which exhibit unique characteristics of self-renewal and multilineage differentiation, have been documented to possess intrinsic resistance to various therapies, encompassing resistance to castration, chemotherapy, and radiotherapy [52]. It has been observed that PCSCs either do not express or exhibit extremely low levels of AR expression, and their proliferation is independent of AR [53]. ADT, along with the suppression of AR expression or activity, has been demonstrated to reprogram bulk PCa cells, leading to the generation of AR-/lo PCSCs [41, 54]. It has been established that numerous signaling pathways, including PI3K/AKT, Notch, hedgehog/GLI, Wnt/β-catenin, and STAT3, may positively regulate the properties of PCSCs [55]. Given that the PI3K/AKT signaling pathway has been previously discussed, the remaining signaling pathways will be examined in detail below, with a focus on causal interpretations and speculations: (1) Notch signaling pathway: In the normal prostate, Notch signaling is thought to govern the differentiation state and structural organization of the gland. Aberrant Notch expression within tissues may promote the development of PCa, with expression levels increasing alongside cancer grade [56]. It has been speculated that HBx within the body could activate the Notch pathway, triggering apoptosis and abnormal cell cycle alterations, ultimately culminating in liver cancer progression [57]. (2) Hedgehog/GLI Signaling Pathway: The Hedgehog signaling pathway is instrumental in maintaining stem cell populations, facilitating tissue repair, and promoting regeneration in normal adult tissues. Aberrant activation of the Hedgehog pathway has been noted in various cancers [58]. With respect to PCa, there is mounting evidence suggesting that Hedgehog signaling plays a pivotal role in the disease's progression towards more aggressive and therapy-resistant states [59]. Glioma-associated oncogene homolog 1 (GLI1), a crucial transcriptional activator of the Hedgehog signaling pathway, when upregulated, fosters the growth and proliferation of these CSCs, such as esophageal squamous cell carcinoma (ESCC), lung squamous cell carcinoma (LSCC), ductal breast carcinoma (DBC), and PCa [60]. It has been established that in HBV-induced liver cancer, HBx activates the Hedgehog pathway through diverse mechanisms: Firstly, HBx can upregulate the expression of GLI1 and GLI2 mRNA and proteins, which serve as master regulators of Hedgehog signaling [40]. Secondly, HBx enhances the protein stability of GLI1 and GLI2 and induces the nuclear translocation of GLI1 through direct protein-protein interaction between HBx and GLI1 [40]. (3) Wnt/β-catenin signaling pathway: wingless-type MMTV integration site family (Wnt) proteins secreted by the tumor stroma contribute to therapy resistance [61]. Moreover, inhibition of androgen activity leads to upregulation of the Wnt/β-catenin pathway, which subsequently promotes androgen-independent growth of PCa cells [36]. In liver cancer cells, HBx activates the Wnt/β-catenin signal pathway through multiple routes, thereby facilitating the initiation, invasion, and metastasis

of liver cancer [37]. (4) STAT3 signaling pathway: The loss of AR expression triggers STAT3 activation in PCa cells, which further leads to the development of PCSCs [54]. The activation of STAT3 induced by AR downregulation is mediated by a high concentration of IL-6 induced by HBx [47, 54].

In addition to the aforementioned factors, several other mechanisms may also contribute to the development of CRPC promoted by HBV infection. First, HBx suppresses the expression of tumor suppressor genes, such as p53, and inhibits the function of negative growth regulators [62]. Second, HBV-DNA integration into the host cell genome occurs at various stages of infection, including during the development of HCC [63], and HBV integration-targeted genes (ITGs) are significantly enriched in many cancer-related signaling pathways, such as the MAPK and Hedgehog pathways [63]. However, whether HBV-DNA integrates into normal prostate cells to promote the development of PCa or integrates into PCa cells to promote the development of CRPC remains unclear and requires further investigation.

There are several limitations to this study. Firstly, this was a retrospective analysis conducted at a single institution. Secondly, there was a small number of patients in the HBsAg-positive group. Thirdly, all patients are of Chinese Han ethnicity. Lastly, since this study is a preliminary one, the mechanisms by which HBV infection promotes the early progression of advanced patients to CRPC after CAB therapy remain speculative and are based solely on existing literature, without experimental validation or mechanistic investigation.

5. Conclusions

Chronic HBV infection was associated with an earlier onset of PCa and a shorter time to progression to CRPC. The mechanism behind this association is unclear and requires further investigation. In patients with advanced PCa who are HBsAg-positive, earlier initiation of intensive treatment combined with closer follow-up may be warranted compared with HBsAg-negative patients.

AVAILABILITY OF DATA AND MATERIALS

All relevant data are within the manuscript and its Supporting Information file (**Supplementary material**).

AUTHOR CONTRIBUTIONS

YW and PG—designed the study, collected and analyzed the data, and wrote the article. HL, YL and ZLC—contributed to the collection and analysis of data. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This research was approved by the Medical Ethics Committee of Neijiang First People's Hospital (Neijiang, China; approval number: 2024-LSP-71). A waiver of informed consent was approved by the Medical Ethics Committee in accordance with Article 39 of the Chinese Ethical Guidelines for Biomedical Research Involving Humans (2016), as this retrospective study posed minimal risk (defined as risks not exceeding those encountered in daily life or routine physical examinations, per Article 39 of the Chinese Guidelines), and contacting participants for consent would compromise the scientific validity of the findings. The authors did not have access to information that could identify individual participants during or after data collection. All procedures adhered to relevant ethical guidelines and regulations.

ACKNOWLEDGMENT

We would like to thank Hu Bingqian from Neijiang Normal University for English language editing.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/files/article/20932241768882339 84/attachment/Supplementary%20material.xlsx.

REFERENCES

[1] Liu X, Yu C, Bi Y, Zhang ZJ. Trends and age-period-cohort effect on incidence and mortality of prostate cancer from 1990 to 2017 in China. Public Health. 2019; 172: 70–80.

[2] Crawford ED. Combined androgen blockade. European Urology. 1996; 29: 54–61.

[3] Lowrance WT, Breau RH, Chou R, Chapin BF, Crispino T, Dreicer R, *et al*. Advanced prostate cancer: AUA/ASTRO/SUO guideline part I. Journal of Urology. 2021; 205: 14–21.

[4] Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, *et al*. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II-2020 update: treatment of relapsing and metastatic prostate cancer. European Urology. 2021; 79: 263–282.

[5] Guo P, Xing X, Wu K, Wang Y, Chen Z, Cao L, *et al*. 1H-MRS study of hippocampus in advanced prostate cancer patients: relationship between hippocampal secondary damage and cognitive disorder following combined androgen blockade therapy. PLOS ONE. 2025; 20: e0323323.

[6] Fukagai T, Namiki TS, Carlile RG, Yoshida H, Namiki M. Comparison of the clinical outcome after hormonal therapy for prostate cancer between Japanese and Caucasian men. BJU International. 2006; 97: 1190–1193.

[7] Hearn JWD, AbuAli G, Reichard CA, Reddy CA, Magi-Galluzzi C, Chang KH, *et al*. HSD3B1 and resistance to androgen-deprivation therapy in prostate cancer: a retrospective, multicohort study. The Lancet Oncology. 2016; 17: 1435–1444.

[8] Agarwal N, Hahn AW, Gill DM, Farnham JM, Poole AI, Cannon-Albright L. Independent validation of effect of HSD3B1 genotype on response to

androgen-deprivation therapy in prostate cancer. JAMA Oncology. 2017; 3: 856–857.

[9] Wu G, Huang S, Nastiuk KL, Li J, Gu J, Wu M, *et al*. Variant allele of HSD3B1 increases progression to castration-resistant prostate cancer. Prostate. 2015; 75: 777–782.

[10] Shiota M, Narita S, Akamatsu S, Fujimoto N, Sumiyoshi T, Fujiwara M, *et al*. Association of missense polymorphism in HSD3B1 with outcomes among men with prostate cancer treated with androgen-deprivation therapy or abiraterone. JAMA Network Open. 2019; 2: e190115.

[11] Iwamoto H, Hori T, Inaba T, Nakagawa R, Kamijima T, Kano H, *et al*. Prognostic impact of time to castration resistance on overall survival in patients with metastatic castration-sensitive prostate cancer. International Journal of Urology. 2025; 32: 1640–1649.

[12] Mesri EA, Feitelson MA, Munger K. Human viral oncogenesis: a cancer hallmarks analysis. Cell Host & Microbe. 2014; 15: 266–282.

[13] Whitaker NJ, Glenn WK, Sahrudin A, Orde MM, Delprado W, Lawson JS. Human papillomavirus and Epstein Barr virus in prostate cancer: koilocytes indicate potential oncogenic influences of human papillomavirus in prostate cancer. Prostate. 2013; 73: 236–241.

[14] Ishiguro H, Furuya K, Izumi K, Nagai T, Kawahara T, Kubota Y, *et al*. Detection of serum hepatitis B virus antigen and hepatitis C virus antibody from prostate cancer patients in Japan. Integrative Molecular Medicine. 2017; 4: 1–3.

[15] Sarkar P, Malik S, Banerjee A, Datta C, Pal DK, Ghosh A, *et al*. Differential microbial signature associated with benign prostatic hyperplasia and prostate cancer. Frontiers in Cellular and Infection Microbiology. 2022; 12: 894777.

[16] Wang H, Men P, Xiao Y, Gao P, Lv M, Yuan Q, *et al*. Hepatitis B infection in the general population of China: a systematic review and meta-analysis. BMC Infectious Diseases. 2019; 19: 811.

[17] Bhimma R, Coovadia HM. Hepatitis B virus-associated nephropathy. American Journal of Nephrology. 2004; 24: 198–211.

[18] Huang Z, Su B, Liu F, Zhang N, Ye Y, Zhang Y, *et al*. YAP1 promotes tumor invasion and metastasis in nasopharyngeal carcinoma with hepatitis B virus infection. OncoTargets and Therapy. 2020; 13: 5629–5642.

[19] Fiorino S, Cuppini A, Castellani G, Bacchi-Reggiani ML, Jovine E. HBV- and HCV-related infections and risk of pancreatic cancer. Journal of the Pancreas. 2013; 14: 603–609.

[20] Kamiza AB, Su FH, Wang WC, Sung FC, Chang SN, Yeh CC. Chronic hepatitis infection is associated with extrahepatic cancer development: a nationwide population-based study in Taiwan. BMC Cancer. 2016; 16: 861.

[21] Lu T, Yang Q, Li M, Zhang J, Zou J, Huang L, *et al*. HBV infection and extra-hepatic cancers in adolescents and 20s: a retrospective study in China. Cancer Epidemiology. 2018; 55: 149–155.

[22] Lin TT, Chen YH, Wu YP, Chen SZ, Li XD, Lin YZ, *et al*. Risk factors for progression to castration-resistant prostate cancer in metastatic prostate cancer patients. Journal of Cancer. 2019; 10: 5608–5613.

[23] Ma Y, Liu Z, Yu W, Huang H, Wang Y, Niu Y. Investigating high-risk factors, precise diagnosis, and treatment of castration- resistant prostate cancer (CRPC). Combinatorial Chemistry & High Throughput Screening. 2024; 27: 2598–2608.

[24] Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, *et al*. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. European Urology. 2017; 71: 630–642.

[25] Frees S, Akamatsu S, Bidnur S, Khalaf D, Chavez-Munoz C, Struss W, *et al*. The impact of time to metastasis on overall survival in patients with prostate cancer. World Journal of Urology. 2018; 36: 1039–1046.

[26] Tang H, Oishi N, Kaneko S, Murakami S. Molecular functions and biological roles of hepatitis B virus x protein. Cancer Science. 2006; 97: 977–983.

[27] Zhu R, Zhang JS, Zhu YZ, Fan J, Mao Y, Chen Q, *et al*. HBx-induced androgen receptor expression in HBV-associated hepatocarcinoma is independent of the methylation status of its promoter. Histology and Histopathology. 2011; 26: 23–35.

[28] Chiu CM, Yeh SH, Chen PJ, Kuo TJ, Chang CJ, Chen PJ, *et al*. Hepatitis B virus X protein enhances androgen receptor-responsive gene expression depending on androgen level. Proceedings of the National Academy of Sciences of the United States of America. 2007; 104: 2571–2578.

[29] Mulholland DJ, Kobayashi N, Ruscetti M, Zhi A, Tran LM, Huang J, *et al*. Pten loss and RAS/MAPK activation cooperate to promote EMT and metastasis initiated from prostate cancer stem/progenitor cells. Cancer Research. 2012; 72: 1878–1889.

[30] Oh JC, Jeong DL, Kim IK, Oh SH. Activation of calcium signaling by hepatitis B virus-X protein in liver cells. Experimental & Molecular Medicine. 2003; 35: 301–309.

[31] Ueda T, Mawji NR, Bruchovsky N, Sadar MD. Ligand-independent activation of the androgen receptor by interleukin-6 and the role of steroid receptor coactivator-1 in prostate cancer cells. Journal of Biological Chemistry. 2002; 277: 38087–38094.

[32] Bekçibaşı M, Deveci Ö, Oğuz A, Bozkurt F, Dayan S, Çelen MK. Serum TNF-α, IL-1β, and IL-6 levels in chronic HBV-infected patients. International Journal of Clinical Practice. 2021; 75: e14292.

[33] Feng S, Tang Q, Sun M, Chun JY, Evans CP, Gao AC. Interleukin-6 increases prostate cancer cells resistance to bicalutamide via TIF2. Molecular Cancer Therapeutics. 2009; 8: 665–671.

[34] Wegiel B, Bjartell A, Culig Z, Persson JL. Interleukin-6 activates PI3K/Akt pathway and regulates cyclin A1 to promote prostate cancer cell survival. International Journal of Cancer. 2008; 122: 1521–1529.

[35] Seo WI, Park S, Gwak J, Ju BG, Chung JI, Kang PM, *et al*. Wnt signaling promotes androgen-independent prostate cancer cell proliferation through up-regulation of the hippo pathway effector YAP. Biochemical and Biophysical Research Communications. 2017; 486: 1034–1039.

[36] Wang C, Chen Q, Xu H. Wnt/β-catenin signal transduction pathway in prostate cancer and associated drug resistance. Discover Oncology. 2021; 12: 40.

[37] Hsieh A, Kim HS, Lim SO, Yu DY, Jung G. Hepatitis B viral X protein interacts with tumor suppressor adenomatous polyposis coli to activate Wnt/β-catenin signaling. Cancer Letters. 2011; 300: 162–172.

[38] Chen M, Feuerstein MA, Levina E, Baghel PS, Carkner RD, Tanner MJ, *et al*. Hedgehog/Gli supports androgen signaling in androgen deprived and androgen independent prostate cancer cells. Molecular Cancer. 2010; 9: 89.

[39] Li N, Chen M, Truong S, Yan C, Buttyan R. Determinants of Gli2 co-activation of wildtype and naturally truncated androgen receptors. Prostate. 2014; 74: 1400–1410.

[40] Kim HY, Cho HK, Hong SP, Cheong J. Hepatitis B virus X protein stimulates the Hedgehog-Gli activation through protein stabilization and nuclear localization of Gli1 in liver cancer cells. Cancer Letters. 2011; 309: 176–184.

[41] Sánchez BG, Bort A, Vara-Ciruelos D, Díaz-Laviada I. Androgen deprivation induces reprogramming of prostate cancer cells to stem-like cells. Cells. 2020; 9: 1441.

[42] Shao DD, Xue W, Krall EB, Bhutkar A, Piccioni F, Wang X, *et al*. KRAS and YAP1 converge to regulate EMT and tumor survival. Cell. 2014; 158: 171–184.

[43] Zhang L, Yang S, Chen X, Stauffer S, Yu F, Lele SM, *et al*. The hippo pathway effector YAP regulates motility, invasion, and castration-resistant growth of prostate cancer cells. Molecular and Cellular Biology. 2015; 35: 1350–1362.

[44] Wang Y, Fang R, Cui M, Zhang W, Bai X, Wang H, *et al*. The oncoprotein HBXIP up-regulates YAP through activation of transcription factor c-Myb to promote growth of liver cancer. Cancer Letters. 2017; 385: 234–242.

[45] Shiota M, Bishop JL, Nip KM, Zardan A, Takeuchi A, Cordonnier T, *et al*. Hsp27 regulates epithelial mesenchymal transition, metastasis, and circulating tumor cells in prostate cancer. Cancer Research. 2013; 73: 3109–3119.

[46] Liu C, Zhu Y, Lou W, Cui Y, Evans CP, Gao AC. Inhibition of constitutively active Stat3 reverses enzalutamide resistance in LNCaP derivative prostate cancer cells. Prostate. 2014; 74: 201–209.

[47] Teng J, Wang X, Xu Z, Tang N. HBx-dependent activation of Twist mediates STAT3 control of epithelium-mesenchymal transition of liver cells. Journal of Cellular Biochemistry. 2013; 114: 1097–1104.

[48] Hill R, Wu H. PTEN, stem cells, and cancer stem cells. Journal of Biological Chemistry. 2009; 284: 11755–11759.

[49] Jiao J, Wang S, Qiao R, Vivanco I, Watson PA, Sawyers CL, *et al*. Murine cell lines derived from Pten null prostate cancer show the critical role

of PTEN in hormone refractory prostate cancer development. Cancer Research. 2007; 67: 6083–6091.

[50] Lee YI, Hwang JM, Im JH, Lee YI, Kim NS, Kim DG, *et al*. Human hepatitis B virus-X protein alters mitochondrial function and physiology in human liver cells. Journal of Biological Chemistry. 2004; 279: 15460–15471.

[51] Ha HL, Yu DY. HBx-induced reactive oxygen species activates hepatocellular carcinogenesis via dysregulation of PTEN/Akt pathway. World Journal of Gastroenterology. 2010; 16: 4932–4937.

[52] Verma P, Shukla N, Kumari S, Ansari MS, Gautam NK, Patel GK. Cancer stem cell in prostate cancer progression, metastasis and therapy resistance. Biochimica et Biophysica Acta. Reviews on Cancer. 2023; 1878: 188887.

[53] Deng Q, Tang DG. Androgen receptor and prostate cancer stem cells: biological mechanisms and clinical implications. Endocrine-Related Cancer. 2015; 22: T209–T220.

[54] Schroeder A, Herrmann A, Cherryholmes G, Kowolik C, Buettner R, Pal S, *et al*. Loss of androgen receptor expression promotes a stem-like cell phenotype in prostate cancer through STAT3 signaling. Cancer Research. 2014; 74: 1227–1237.

[55] Zong Y, Goldstein AS. Adaptation or selection—mechanisms of castration-resistant prostate cancer. Nature Reviews Urology. 2013; 10: 90–98.

[56] Deng G, Ma L, Meng Q, Ju X, Jiang K, Jiang P, *et al*. Notch signaling in the prostate: critical roles during development and in the hallmarks of prostate cancer biology. Journal of Cancer Research and Clinical Oncology. 2016; 142: 531–547.

[57] Kongkavitoon P, Tangkijvanich P, Hirankarn N, Palaga T. Hepatitis B virus HBx activates notch signaling via delta-like 4/notch1 in hepatocellular carcinoma. PLOS ONE. 2016; 11: e0146696.

[58] Yang L, Xie G, Fan Q, Xie J. Activation of the hedgehog-signaling pathway in human cancer and the clinical implications. Oncogene. 2010; 29: 469–481.

[59] Kim TJ, Lee JY, Hwang TK, Kang CS, Choi YJ. Hedgehog signaling protein expression and its association with prognostic parameters in prostate cancer: a retrospective study from the view point of new 2010 anatomic stage/prognostic groups. Journal of Surgical Oncology. 2011; 104: 472–479.

[60] Lv L, Yang Z, Ma T, Xuan Y. Gli1, a potential cancer stem cell marker, is strongly associated with prognosis in prostate cancer. International Journal of Clinical and Experimental Pathology. 2018; 11: 4957–4966.

[61] Murillo-Garzón V, Kypta R. WNT signalling in prostate cancer. Nature Reviews Urology. 2017; 14: 683–696.

[62] Su JM, Lai XM, Lan KH, Li CP, Chao Y, Yen SH, *et al*. X protein of hepatitis B virus functions as a transcriptional corepressor on the human telomerase promoter. Hepatology. 2007; 46: 402–413.

[63] Yang L, Ye S, Zhao X, Ji L, Zhang Y, Zhou P, *et al*. Molecular Characterization of HBV DNA Integration in Patients with Hepatitis and Hepatocellular Carcinoma. Journal of Cancer. 2018; 9: 3225–3235.

How to cite this article: Yu Wang, Huan Liao, Yi Liu, Zhili Cheng, Peng Guo. Relationship between chronic hepatitis B virus infection and tumor progression in Chinese patients with advanced prostate cancer following combined androgen blockade therapy: a retrospective cohort study. Journal of Men's Health. 2026; 22(8): 75-86. doi: 10.22514/jomh.2026.069.