

Serum hepatitis B viral (HBV) DNA is a predictive biomarker for survival in non-small cell lung cancer patients with chronic HBV infection

This article was published in the following Dove Press journal:
Cancer Management and Research

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Purpose: To study the association between pretreatment serum hepatitis B viral (HBV) DNA copy numbers and clinical outcome of non-small cell lung cancer (NSCLC) patients with chronic HBV infection.

Patients and methods: We retrospectively evaluated the medical records of NSCLC HBV (+) patients between January 2008 and December 2010. The HBV DNA copy numbers and other prognostic factors including albumin (ALB), C-reactive protein (CRP), platelet, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and Glasgow Prognostic Score (GPS) were obtained before any antitumor treatment. Kaplan-Meier curves and the log-rank test were used to calculate prognostic significance. A multivariable Cox proportional hazard regression was modeled to analyze the independent prognostic factors for NSCLC HBV (+) patients. All independent prognostic factors in the Cox multivariable analysis were used to build a nomogram. The predictive accuracy of HBV DNA, TNM stage and nomogram was evaluated with the concordance index (C-index) and time-dependent receiver operating characteristics (ROC) curves, and simultaneously compared with traditional TNM staging system respectively.

Results: A total of 188 patients were recruited in this study; the median age was 56 years, and the median overall survival (OS) was 34 months. Cox multivariate analysis results showed independent factors for OS including TNM stage ($P=0.028$), treatment ($P=0.002$), HBV DNA ($P<0.001$), and GPS ($P=0.026$). The nomogram model for survival was built based on four prognostic factors. The C-index for HBV DNA was 0.67, 0.69 for TNM stage, and 0.76 for the nomogram model. There was no statistical difference between HBV DNA and TNM stage ($P=0.48$). However, the C-index values of nomogram model were statistically higher both than HBV DNA (0.76 vs 0.67, $P<0.001$), and TNM stage (0.76 vs 0.69, $P<0.001$).

Conclusion: Pretreatment serum HBV DNA copy numbers can act as a prognostic marker of survival for NSCLC patients with chronic HBV infection.

Keywords: non-small cell lung cancer, hepatitis B, hepatitis B viral DNA, HBV DNA, nomogram, prognosis

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Introduction

Lung cancer is the commonest and most fatal of all cancers worldwide. The 5-year overall survival (OS) rate is estimated at 18%.¹ Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, and accounts for approximately 85% of all lung cancer cases.²

A chronic hepatitis B (CHB) infection typically induces prolonged inflammation.³ Chronic inflammation can lead to carcinogenesis; there is evidence that inflammation can

affect the proliferation and survival of malignant cells, angiogenesis, tumor initiation and metastasis, and tumor response to drugs.^{4,5} Moreover, hepatitis B viral (HBV) infection is associated with poorer outcomes for hepatocellular,⁶ pancreatic carcinoma,⁷ nasopharyngeal carcinoma,⁸ and NSCLC cases.⁹ This finding may imply that investigation of a new prognostic model is required in HBV-positive NSCLC patients.

Many studies have reported that the serum level of HBV DNA correlates with the progression of hepatocellular carcinoma (HCC).¹⁰ No studies, however, have explored the influence of serum HBV DNA on the progression of NSCLC. Therefore, it is necessary to determine the ability of HBV DNA to predict the outcome of HBV-positive NSCLC patients, to both improve and optimize therapies.

The American Joint Committee on Cancer (AJCC) TNM classification is the current standard for determining treatment schemes for many cancer patients. However, because of the heterogeneous nature of cancer, differences in clinical outcomes may arise in cancer patients with the same TNM stage receiving similar treatment strategies.¹¹ This indicates that further research is needed to explore more functional biomarkers which are able to improve prognosis prediction of cancer. Numerous risk factors, such as age,¹² sex,¹³ smoking status,¹⁴ albumin (ALB), C-reactive protein (CRP),¹⁵ neutrophil–lymphocyte ratio (NLR),¹⁶ platelet–lymphocyte ratio (PLR),¹⁶ and Glasgow Prognostic Score (GPS)¹⁷ have been reported to be prognostic factors for lung cancer. Nomograms are widely used to predict cancer prognosis for an individual patient.¹⁸ Moreover, a nomogram could have several advantages over the TNM stage.^{19–21}

The purpose of the present study is to evaluate the ability of HBV DNA in combination with inflammatory markers and clinicopathological prognostic factors to predict outcomes for NSCLC patients with HBV infection. Notably, we develop a nomogram-based risk prediction model and compare the predictive power of HBV DNA and the nomogram model with conventional TNM staging.

Material and methods

Patients and study design

The present study was approved by the Clinical Research Ethics Committee of Liwan Hospital of the Third Affiliated Hospital of Guangzhou Medicine University and Sun Yat-sen University Cancer Center (Guangzhou, China). Informed consent was provided by each included patient. We performed a retrospective review of NSCLC patients with chronic HBV infection from Liwan Hospital of the Third Affiliated Hospital

of Guangzhou Medicine University and Sun Yat-sen University Cancer Center between January 2008 and December 2010. The inclusion criteria as follows. All patients were newly diagnosed and histologically confirmed as NSCLC; all patients had HBsAg (+); and had no fibrosis, steatosis or cirrhosis of the liver. Patients were excluded if they were diagnosed with malignancies other than NSCLC, had acute hepatitis, or had hepatitis A or hepatitis C infection or had incomplete clinical pathological data.

The following information was obtained from the patients' medical records: patient's name, gender, age, family history of cancer, smoking status, TNM stage (according to the 7th edition of AJCC TNM staging manual), histological type, tumor diameter, and treatment. Patients' serum HBV DNA, ALB, CRP, platelet, NLR, PLR, and GPS were obtained before anti-tumor treatment.

The inflammation-based prognostic factors were defined and calculated as follows: GPS: patients with both CRP >10 mg/L and ALB <35 g/L were allocated a score of 2; patients with CRP >10 mg/L or ALB <35 g/L were allocated a score of 1; and patients with neither of these abnormalities were categorized as having a score of 0.²²

All continuous variables were transformed into categorical variables based on the optimal cutoff values. These were each 10-fold increase in HBV DNA level or the median values for age (56 years), tumor size (4.0 cm), ALB (42.0 g/L), CRP (4.0 mg/L), platelet (229×10^9 /L), NLR (2.23), and PLR (121.5).

Overall survival (OS) was defined time from the date of the diagnosis until the date of death, or the deadline. Patient follow-up was complete up to January 2016.

Statistical analyses

Statistical analyses were performed with SPSS Statistics 19.0 (IBM Corporation, Armonk, NY, USA) and R version 3.5.1 (Institute of Statistics and Mathematics, Vienna, Austria). Survival curves were depicted using the Kaplan–Meier curve with log-rank test, to calculate the prognostic significance. All prognostic factors with $P < 0.05$ in the univariable analysis were included as covariates in the multivariable Cox proportional hazard regression to determine the independent prognostic factors for NSCLC patients with chronic HBV infection. The nomogram was built on the results of the Cox regression. The predictive accuracy and discrimination of HBV DNA, TNM stage and nomogram were compared using Harrell's concordance index (C-index)²³ and time-dependent receiver operative characteristics (ROC) curve.²⁴ A larger C-index and area under curve (AUC) of ROC indicated more accurate

prognostic stratification. A two-sided $P < 0.05$ was of statistical significance.

Results

Baseline clinical and characteristics

In accordance with our selection criteria, a total of 188 HBV-positive NSCLC patients were eligible for this study. Of these, 144 (76.6%) were male and 44 (23.4%) were female. The median age and OS were 56 years (27–82 years) and 34 months (range =1–82 months), respectively. Based on the concentrations of HBV DNA (copies/mL), the 188 patients were divided into five groups containing $<10^3$ (60, 31.9%), 10^3 –9,999 (49, 26.1%), 10^4 –99,999 (30, 16.0%), 10^5 –999,999 (22, 11.7%), and $\geq 10^6$ (27, 14.3%) respectively. Baseline characteristics of these patients are listed in Table 1.

Univariable and multivariable analysis

Univariable survival analysis showed that TNM stage, tumor size, treatment, HBV DNA, ALB, CRP, NLR, and GPS were associated with the OS of HBV-positive NSCLC patients (Table 2). In the multivariable Cox proportional hazard regression, results continued to demonstrate that independent factors for OS including TNM stage (HR: 1.36; 95% CI: 1.03–1.78, $P=0.028$), treatment (HR: 1.57; 95% CI: 1.17–2.09, $P=0.002$), HBV DNA (HR: 1.43; 95% CI: 1.23–1.67, $P < 0.001$), and GPS (HR: 1.69; 95% CI: 1.07–2.69, $P=0.026$) (Table 2). A forest plot showing the hazard ratios and 95% confidence intervals

Table 1 Baseline clinical and characteristics of patients

Characteristic	No.	%
Gender		
Male	144	76.6
Female	44	23.4
Age (years)		
<56	87	46.3
≥ 56	101	53.7
Family history		
Yes	43	22.9
No	145	77.1
Smoking		
Yes	114	60.6
No	74	39.4

(Continued)

Table 1 (Continued).

Characteristic	No.	%
TNM stage ^a		
I	41	21.8
II	19	10.1
III	73	38.8
IV	55	29.3
Histological type		
Adenocarcinoma	119	63.3
Squamous cell carcinoma	62	33.0
Other	7	3.7
Size (cm) ^b		
<4.0	72	38.3
≥ 4.0	116	61.7
Treatment		
Surgery	42	22.3
Surgery and radiotherapy/chemotherapy	63	33.5
Radiotherapy/chemotherapy	61	32.4
Other	22	11.8
HBV DNA, copies/mL		
$<10^3$	60	31.9
10^3 –9,999	49	26.1
10^4 –99,999	30	16.0
10^5 –999,999	22	11.7
$\geq 10^6$	27	14.3
ALB (g/L)		
<42.0	86	45.7
≥ 42.0	102	54.3
CRP (mg/L)		
<4.0	87	46.3
≥ 4.0	101	53.7
Platelet ($10^9/L$)		
<229	93	49.5
≥ 229	95	50.5
NLR		
<2.23	94	50.0
≥ 2.23	94	50.0
PLR		
<121.5	94	50.0
≥ 121.5	94	50.0
GPS		
0	128	68.1
1	53	28.2
2	7	3.7

Notes: ^aTNM stage was classified according to the AJCC 7th TNM staging system; ^bThe tumor maximum diameter.

Abbreviations: TNM, pathological tumor node metastasis stage; ALB, albumin; CRP, C-reactive protein; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; GPS, Glasgow prognostic score; AJCC, American Joint Committee on cancer.

Table 2 Univariable and multivariable analysis for OS

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Gender			-	-
Male	Reference			
Female	0.86 (0.54–1.39)	0.548		
Age (years)			-	-
<56	Reference			
≥56	0.75 (0.50–1.12)	0.159		
Family history			-	-
Yes	Reference			
No	1.04 (0.64–1.67)	0.879		
Smoking			-	-
Yes	Reference			
No	1.05 (0.69–1.58)	0.834		
TNM stage			1.36 (1.03–1.78)	0.028
I	Reference			
II	2.27 (0.89–5.75)	0.085		
III	3.25 (1.61–6.57)	0.001		
IV	7.31 (3.60–14.84)	<0.001		
Histological type			-	-
Adenocarcinoma	Reference			
Squamous cell carcinoma	0.96 (0.62–1.48)	0.845		
Other	2.00 (0.73–5.52)	0.179		
Size (cm)			-	-
<4.0	Reference			
≥4.0	1.83 (1.18–2.84)	0.007		
Treatment			1.57 (1.17–2.09)	0.002
Surgery	Reference			
Surgery and radiotherapy/chemotherapy	0.86 (0.45–1.640)	0.639		
Radiotherapy/chemotherapy	3.21 (1.77–5.83)	<0.001		
Other	6.61 (3.29–13.30)	<0.001		
HBV DNA, copies/mL				

(Continued)

Table 2 (Continued).

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
<103	Reference		1.43 (1.23–1.67)	<0.001
103–9,999	2.00 (1.09–3.70)	0.026		
104–99,999	2.54 (1.34–4.82)	0.004		
105–999,999	4.23 (2.06–8.72)	<0.001		
≥106	6.11 (3.23–11.56)	<0.001		
ALB (g/L)			-	-
<42.0	Reference		-	-
≥42.0	0.60 (0.40–0.90)	0.012		
CRP (mg/L)			-	-
<4.0	Reference			
≥4.0	2.00 (1.31–3.01)	0.001		
Platelet (10 ⁹ /L)				
<229	Reference			
≥229	1.13 (0.75–1.69)	0.562		
NLR			-	-
<2.23	Reference			
≥2.23	1.58 (1.05–2.37)	0.027		
PLR			-	-
<121.5	Reference			
≥121.5	1.29 (0.86–1.93)	0.217		
GPS			1.69 (1.07–2.69)	0.026
0	Reference			
1	2.31 (1.51–3.54)	<0.001		
2	2.35 (0.94–5.88)	0.068		

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; TNM, Pathological Tumor Node Metastasis stage; ALB, albumin; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; GPS, Glasgow prognostic score.

for OS according to the multivariate Cox proportional hazard results is presented in [Figure 1](#).

Survival analysis

Kaplan–Meier curves and the log-rank test were used to calculate prognostic significance. The results showed that serum HBV DNA levels significantly affected OS ($P<0.001$, [Figure 2D](#)). The 1-year OS rates for the patients with serum HBV DNA $<10^3$, 10^3 –9,999, 10^4 –99,999, 10^5 –999,999, and $\geq 10^6$

were 90.0%, 83.7%, 83.3%, 68.2%, and 55.6%, respectively ($P=0.005$, [Figure 2A](#)). The 3-year OS rates were 73.3%, 44.9%, 56.7%, 18.2%, and 14.8%, respectively ($P<0.001$, [Figure 2B](#)). The 5-year OS rates were 60.0%, 28.6%, 23.3%, 4.5%, and 7.4%, respectively ($P<0.001$, [Figure 2C](#)).

Prognostic nomogram for OS

We constructed a prognostic nomogram model incorporating all significant independent factors for OS based on

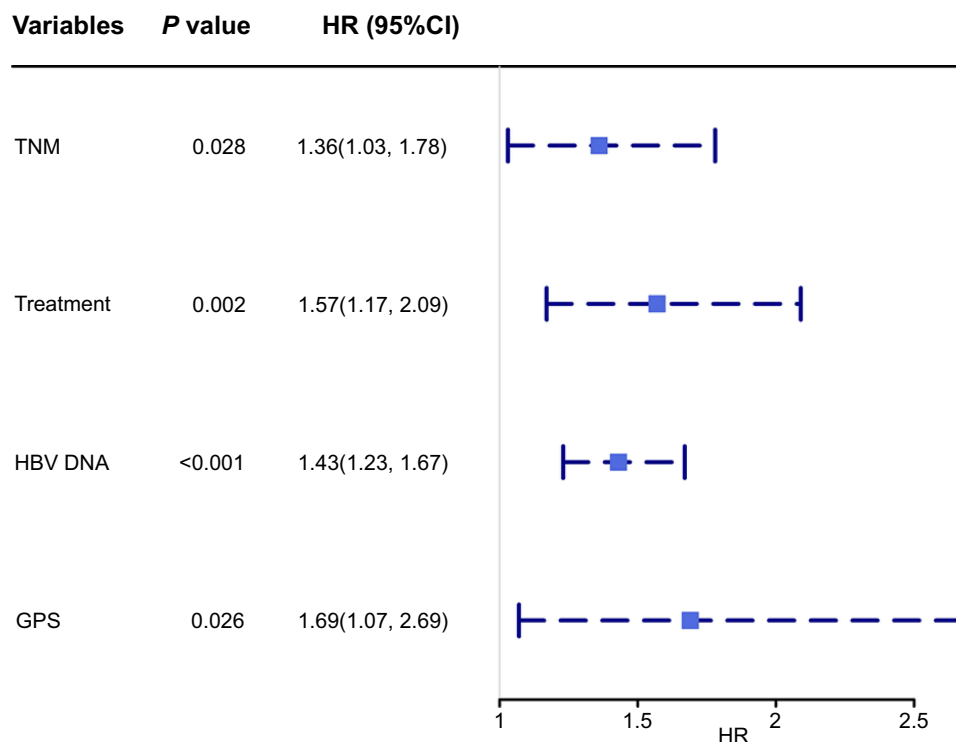


Figure 1 Cox regression forest plot of independent prognostic factors in NSCLC patients with chronic HBV infection.
Abbreviations: HBV, hepatitis B viral; GPS, Glasgow Prognostic Score; NSCLC, non-small cell lung cancer.

multivariable Cox proportional hazards results, and further visualized it as shown in Figure 3. Each prognostic factor was assigned a point. By summing up the risk points from all the variables and locating it to the total points scale, we could determine the 1-, 3- and 5-year OS probability of a specific patient by drawing a vertical line from “Total Points” towards the axis labeled “1-, 3- and 5-year survival”. The prognostic nomogram model showed that serum HBV DNA was considered to be the most promising potential biomarker to complement TNM stage.

Comparison of predictive accuracy between independent factors and nomogram model

The C-indices for TNM stage, treatment, HBV DNA, GPS, and the nomogram model were 0.69 (95% CI: 0.64–0.73), 0.68 (95% CI: 0.63–0.74), 0.67 (95% CI: 0.61–0.72), 0.61 (95% CI: 0.56–0.66), and 0.76 (95% CI: 0.72–0.81), respectively. The nomogram model showed much higher results than the TNM stage (0.76 vs 0.69, $P<0.001$) and HBV DNA (0.76 vs 0.67, $P<0.001$). These results indicated the nomogram model had greater predictive accuracy. However, there was no statistical difference between HBV

DNA and TNM stage (0.67 vs 0.69, $P=0.48$), treatment (0.67 vs 0.68, $P=0.50$), and GPS (0.67 vs 0.61, $P=0.12$). The results are listed in Table 3. No significant difference was observed when comparing the area under curves (AUCs) of time-dependent ROC curve between HBV DNA and TNM stage, treatment, and GPS (Figure 4).

Discussion

In this study, we retrospectively evaluated the prognostic role of serum HBV DNA in NSCLC patients with chronic HBV infection. Our results indicated that HBV DNA is an independent prognostic marker for the HBV-positive NSCLC patients based on both univariable and multivariable analyses. Patients with high levels of HBV DNA have poor prognosis. Accordingly, this finding highlights the importance of baseline serum HBV DNA for predicting outcomes, and thus suggests that cancer therapy should be combined with antiviral therapy in NSCLC patients with hepatitis B. In addition, we also create a prognostic nomogram model for OS in HBV-positive NSCLC patients, which including HBV DNA, TNM stage, treatment, and GPS. This nomogram has more predictive accuracy than TNM stage.

HBV infection, as an independent prognostic factor, has been reported in patients with hepatocellular,

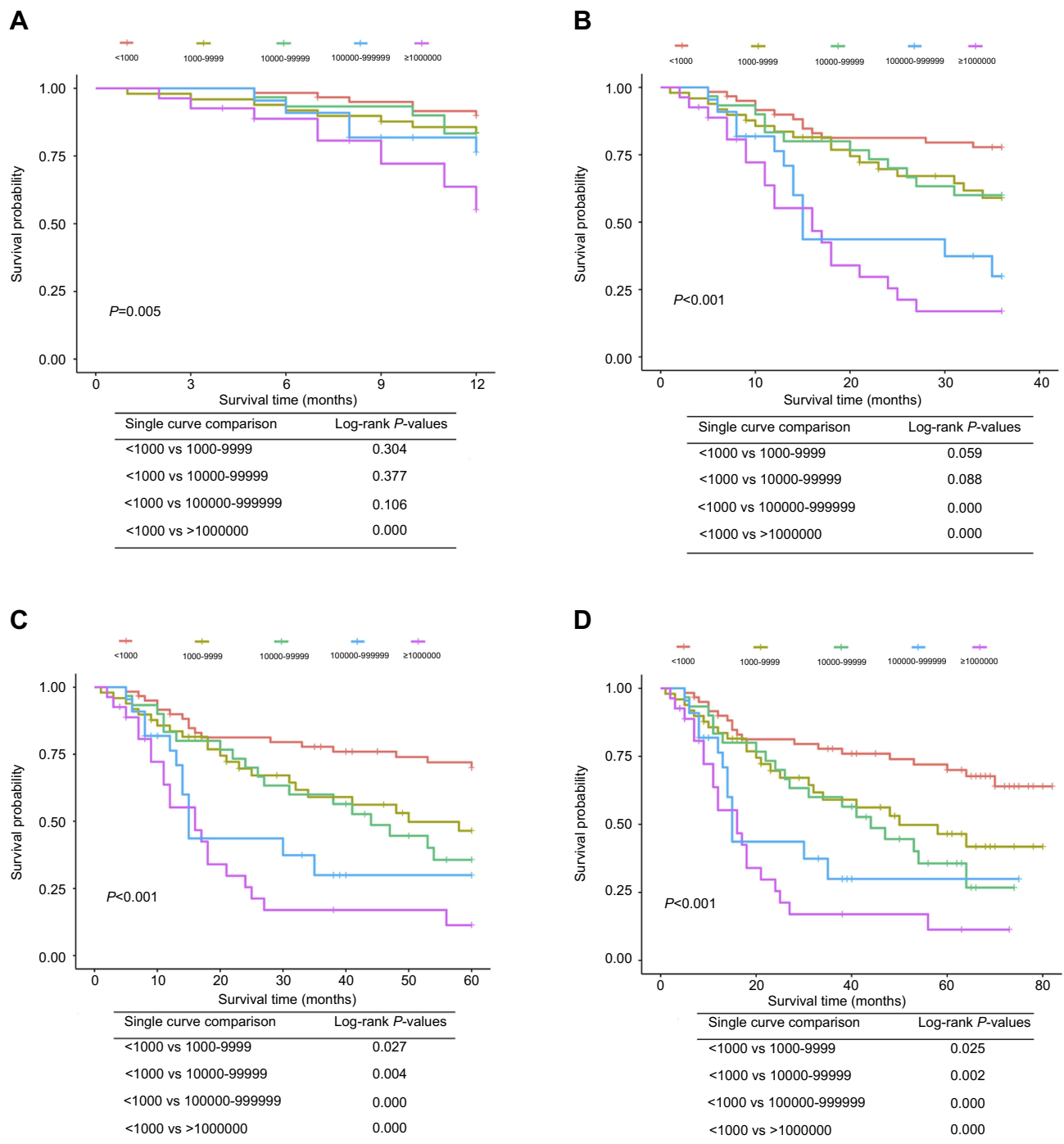


Figure 2 Kaplan–Meier estimates of 1-, 3-, and 5-year survival and OS for NSCLC patients with different HBV DNA levels. **(A)** 1-year survival; **(B)** 3-year survival; **(C)** 5-year survival; **(D)** OS for NSCLC patients.

Abbreviations: HBV, hepatitis B viral; NSCLC, non-small cell lung cancer; OS, overall survival.

pancreatic carcinoma, nasopharyngeal carcinoma, and NSCLC. Chen et al established a prognostic nomogram model for OS in HBV-positive NSCLC patients based on liver function markers²⁵ and inflammation-based factors,²⁶ but did not include the HBV DNA levels. Interestingly, our study incorporated HBV DNA copy numbers, clinico-pathologic factors, and inflammation-based prognostic

factors into the TNM staging system to establish a nomogram model, which has a better predictive accuracy and discriminative ability than HBV DNA alone and TNM stage. Our results could help clinicians with decision-making and clinical consultations.

The molecular mechanisms underlying the influence of HBV on the outcome of NSCLC patients are not

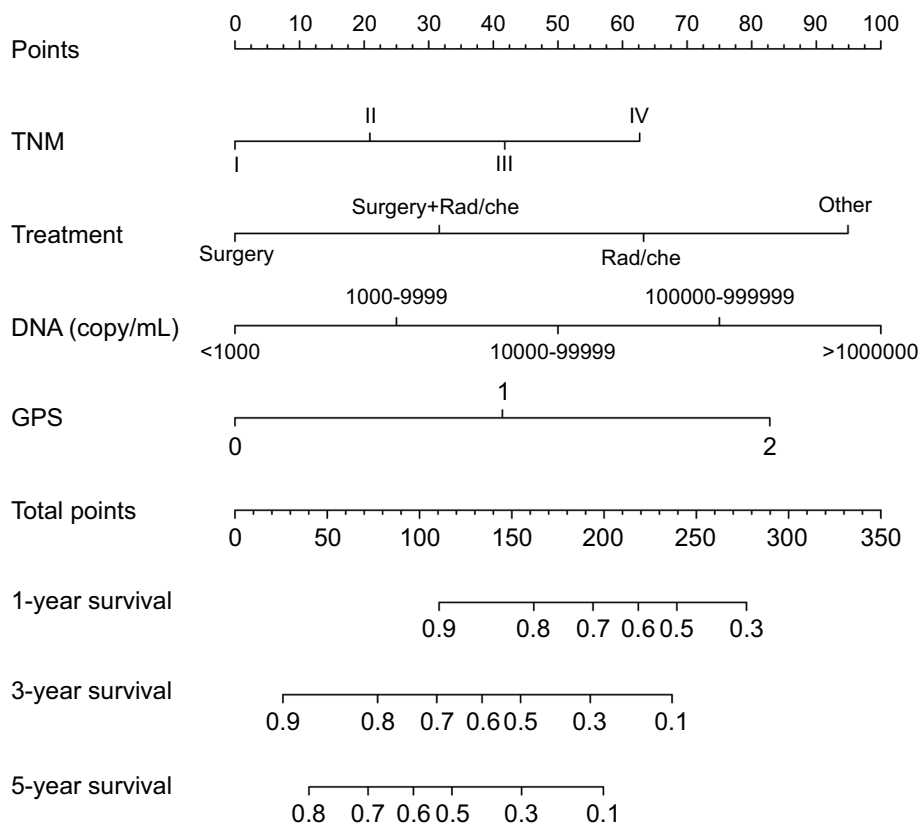


Figure 3 Nomogram model predicting 1-, 3- and 5-year survival in NSCLC patients with chronic HBV infection.

Abbreviations: GPS, Glasgow Prognostic Score; HBV, hepatitis B viral; NSCLC, non-small cell lung cancer; Rad/che, radiotherapy/chemotherapy.

Table 3 The C-index of independent factors and nomogram for prediction of OS*

Factor	C-index (95% CI)	P
Nomogram*	0.76 (0.72–0.81)	
TNM stage	0.69 (0.64–0.73)	
Treatment	0.68 (0.63–0.74)	
HBV DNA	0.67 (0.61–0.72)	
GPS	0.61 (0.56–0.66)	
HBV DNA vs nomogram		<0.001
TNM stage vs nomogram		<0.001
HBV DNA vs treatment		0.50
HBV DNA vs GPS		0.12
HBV DNA vs TNM stage		0.48

Note: *Nomogram: including four risk factors (TNM, treatment, HBV DNA, and GPS).

Abbreviations: C-index, concordance index; GPS, Glasgow Prognostic Score; HBV, hepatitis B viral; OS, overall survival.

understood. There are several possible explanations. Firstly, the interaction of HBV and the host immune system could lead to nonresolving inflammation,²⁷ which could activate transcription factors (NF- κ B, STAT3), and then promote the production of cytokines and chemokines.^{28,29} These aid in the proliferation and

survival of malignant cells, and promote angiogenesis and metastasis.³⁰ Secondly, HBV had been detected in extrahepatic tissue and diverse cell types, which means HBV could also exist in the lung.³¹ Prolonged exposure to HBV may promote cancer proliferation, invasion, and metastasis.^{32,33} Finally, the hepatitis B virus X protein (HBx) is a small 17-kDa soluble protein in the nucleus and cytoplasm of host cells,³⁴ that is closely related to the carcinogenesis of HCC.³⁵ Some studies have shown significant alteration in expression of lncRNA, microRNA and mRNA induced by HBx in liver cell lines.^{36,37} Many of the above molecules displayed diverse biological functions, such as gene expression, DNA replication, DNA repair, cell cycle, cell division, cell–cell signaling, cell adhesion, signal transduction, and cell surface receptor signaling pathway.³⁷ These molecules may enter the blood circulation to the lung, where they could promote tumor growth and progression.

There are several limitations to our study. First of all, it was a retrospective study, and thus a selection bias cannot be fully excluded. Secondly, all the data came from a single institute with a relatively small sample size. Therefore,

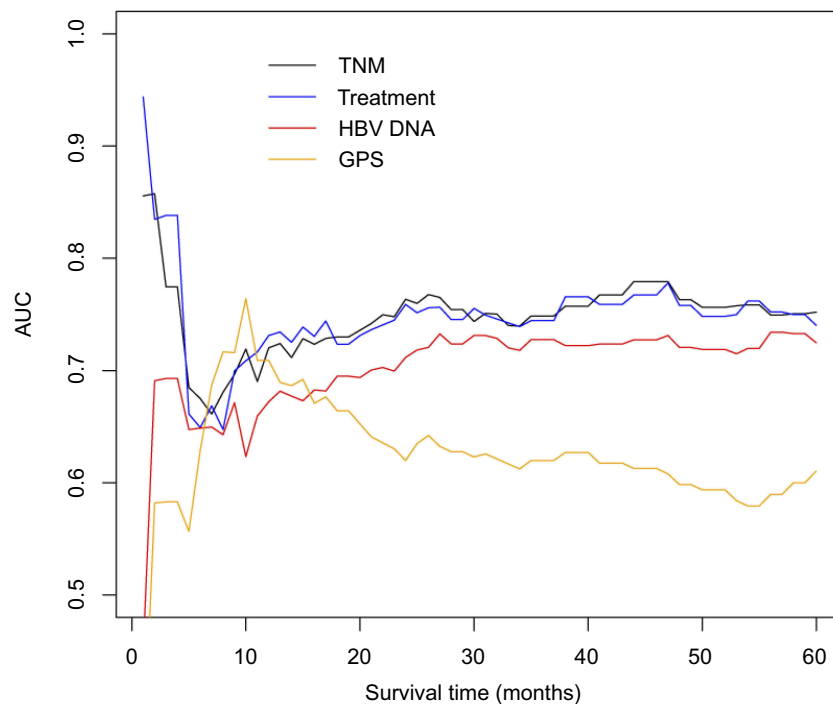


Figure 4 Time-dependent ROC analysis of TNM, treatment, HBV DNA, and GPS.

Abbreviations: AUC, area under the curve; GPS, Glasgow Prognostic Score; HBV, hepatitis B viral; ROC, receiver operating characteristic.

external multi-institute validation is needed in the future. Third, information on post-antiviral drug intake was insufficient. Finally, other potential prognostic factors such as cytokeratin 19 fragment (CYFRA21-1), carcinoembryonic antigen (CEA), and epidermal growth factor receptor (EGFR) were not assessed.^{38,39} In the future, more studies are needed to confirm the mechanisms underlying the observed influence of HBV on the survival outcomes of NSCLC patients.

In conclusion, our study demonstrates that pretreatment serum HBV DNA is an independent prognostic marker for NSCLC patients with chronic HBV infection. Higher copy numbers were linked with poor prognosis. The predictive accuracy of HBV DNA was equivalent to TNM stage. A prognostic nomogram based on HBV DNA, TNM stage, treatment, and GPS could enhance the ability to predict OS for HBV-positive NSCLC patients.

Acknowledgments

We thank the staff at the Laboratory Department of Liwan Hospital of The Third Affiliated Hospital of Guangzhou Medicine University, and the Director of Clinical Laboratories, Sun Yat-sen University Cancer Center for providing support on research conditions in this study.

Disclosure

The authors report no conflicts of interest in this work.

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