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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Cohort Study

Serum hepatitis B core-related antigen as a surrogate marker of hepatitis B e antigen seroconversion in chronic hepatitis B

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Abstract

BACKGROUND

Quantitative hepatitis B core-related antigen (qHBcrAg) has a better correlation with intrahepatic hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) than HBV DNA or hepatitis B e antigen (HBeAg), but data are still lacking for its clinical application.

AIM

The aim was to investigate serum qHBcrAg levels in patients with chronic hepatitis B and assess the correlation of serum qHBcrAg with pregenomic RNA (pgRNA), cccDNA, and HBeAg seroconversion.

METHODS

This study was a secondary analysis of patients who underwent percutaneous liver biopsy between July 2014 and June 2019 in two multicenter randomized controlled clinical trials of peginterferon *vs* nucleos(t)ide analog (NUC)-based therapy (NCT03509688 and NCT03546530). Serum qHBcrAg, pgRNA, HBV DNA, hepatitis B core antigen, HBeAg, liver cccDNA, and HBV DNA were measured. The correlations of serum qHBcrAg with other biomarkers were analyzed.

RESULTS

A total of 139 patients were included. The mean qHBcrAg levels were 5.32 ± 1.18 $\log_{10}$ U/mL at baseline and decreased during treatment (all $P < 0.0001$). Serum qHBcrAg levels were positively correlated with pgRNA ($r = 0.597$, $P < 0.0001$) and cccDNA ($r = 0.527$, $P < 0.0001$) levels. The correlation of serum qHBcrAg level and

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intrahepatic HBV DNA levels at baseline was weak but significant (r = 0.399, P < 0.0001). HBcrAg predicted HBeAg seroconversion, with areas under the receiver operating characteristics curve of 0.788 at 24 wk and 0.825 at 48 wk. Log HBcrAg at wk 24 and 48 was independently associated with HBeAg seroconversion [odds ratio (OR) = 2.402, 95% confidence interval (CI): 1.314-4.391, P = 0.004; OR = 3.587, 95%CI: 1.315-9.784, P = 0.013].

CONCLUSION

Serum HBcrAg levels were correlated with HBV virological markers and could be used to predict HBeAg seroconversion.

Key Words: Hepatitis B virus; Hepatitis B core antigen; Hepatitis B virus DNA; Detection; Liver biopsy; Pregenomic RNA; Quantitative hepatitis B core-related antigen; Receiver operating characteristic; Seroconversion; Correlation

Core Tip: The mean quantitative hepatitis B core-related antigen (qHBcrAg) levels were decreased post treatment. Serum qHBcrAg levels were positively associated with pregenomic RNA and covalently closed circular DNA levels. qHBcrAg predicted hepatitis B e antigen (HBeAg) seroconversion with an area under the receiver operating characteristics curve of 0.788 at 24 wk and 0.825 at 48 wk. Log qHBcrAg at wk 24 and wk 48 was independently associated with HBeAg seroconversion (odds ratio = 2.402, 95% confidence interval: 1.314-4.391, P = 0.004; odds ratio = 3.587, 95% confidence interval: 1.315-9.784, P = 0.013, respectively).

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INTRODUCTION

Chronic hepatitis B (CHB) is a liver disease caused by a chronic infection with the hepatitis B virus (HBV) and is potentially life-threatening. CHB is a global health problem that affects about 250 million people worldwide, with a prevalence of < 2% in the United States and other Western countries and > 5% in East Asia, Southeast Asia, and sub-Saharan Africa[1-3]. The disease is particularly endemic in China, where there are about 84 million individuals infected with HBV[4], with a prevalence as high as 6.3% in some rural areas[5]. All-cause mortality associated with HBV infection is about 6%-8%, and 15%-40% of untreated patients with CHB develop serious conditions such as cirrhosis and hepatocellular carcinoma[3,6].

The HBV genome exists in the nuclei of infected hepatocytes as a 3.2-kb double-stranded episomal DNA called covalently closed circular DNA (cccDNA). cccDNA is a key component in the HBV life cycle since it is the template for all viral genomic and subgenomic transcripts, including pregenomic RNA (pgRNA), and its level is correlated with the proliferative potential of HBV[7]. cccDNA serves as the template for pgRNA production, which is the main step in HBV replication[7]. The control of intrahepatic levels of HBV cccDNA and/or controlling the transcriptional activity of cccDNA are critical to prevent the occurrence of decompensated cirrhosis and hepatocellular carcinoma, which is the ultimate goal of anti-HBV therapies[8,9]. Hence, changes in the intrahepatic level of cccDNA can be used to monitor the efficacy of antiviral therapies and evaluate the possibility of viral rebound after stopping treatment[10-12]. The direct method to measure liver cccDNA levels is liver biopsy, but it is an invasive procedure not easily accepted by the patients[13]. Therefore, searching for surrogate indicators of intrahepatic HBV cccDNA is important to optimize patient management and quality of life.

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Although sustained serum HBV DNA suppression and hepatitis B e antigen (HBeAg) seroconversion are associated with disease remission[8], their performance in reflecting the changes in intrahepatic cccDNA is poor[14,15]. Hepatitis B core-related antigen (HBcrAg) is an emerging marker of HBV DNA suppression[16,17]. HBcrAg consists of hepatitis B core antigen (HBcAg), HBeAg, and p22cr. HBcAg and HBeAg share the first 149 amino acids (aa) encoded by the core gene, overlapping the -10 to 183 aa region[18]. A study showed that quantitative HBcrAg (qHBcrAg) better reflects intrahepatic cccDNA levels than HBV DNA or HBeAg[15]. In addition, intrahepatic cccDNA can be determined with an enzyme immunoassay for HBcrAg[19,20]. Nevertheless, HBcrAg is still not widely used by clinicians worldwide because not enough data are currently available.

Therefore, this study aimed to investigate the serum qHBcrAg levels of patients with CHB and assess the correlation of serum qHBcrAg with pgRNA, cccDNA, and HBeAg seroconversion. The results will add to the sparse literature about qHBcrAg and could eventually lead to its wider use in the clinical setting.

MATERIALS AND METHODS

Study design and patients

This study was a secondary analysis of a cohort of patients who underwent percutaneous liver biopsy at baseline and after 48 wk of therapy between July 2014 and June 2019 during their participation in two multicenter randomized controlled clinical trials of peginterferon (Peg-IFN) or nucleos(t)ide analog (NUC)-based therapy. The study was approved by the ethics committee of the First Hospital of Jilin University. Informed consent was obtained from each patient for the original trials, with clauses for possible secondary analyses. The original studies were registered (ClinicalTrials.gov NCT03509688 and NCT03546530).

All patients were diagnosed with CHB according to the criteria of detectable HBV DNA ≥ 10^5 IU/mL, alanine aminotransferase (ALT) 1.5-10 times the upper limit of normal, and HBeAg positivity[3,6]. The inclusion criteria were: (1) Diagnosis of CHB; (2) Treatment with Peg-IFN or NUC-based therapy for at least 48 wk; and (3) Available serum samples and liver specimens at baseline and 48 wk. The exclusion criteria were: (1) A history of hepatitis C virus or hepatitis D virus infection; (2) Human immunodeficiency virus; (3) Inflammatory diseases such as rheumatoid arthritis, diabetes, autoimmune hepatitis, hypertension, or kidney disease; or (4) Recent infectious disease.

Treatment

The treatment regimens followed the clinical practice guidelines OF the Asian-Pacific Association for the Study of the Liver on the management of hepatitis B[21]. In one of the original trials, the patients received entecavir (ETV) (Cosunter Pharmaceutical, China) 0.5 mg once daily po for 144 wk with/without resveratrol 1000 mg once daily for 48 wk or thymosin α1 twice-weekly sc for 24 wk. In the other trial, the patients received interferon (IFN, Kawin Technology, China) 1.5 μg/kg per week sc for 48 wk with/without resveratrol 1000 mg once daily for 48 wk. The patients who underwent liver biopsy before and after 48 wk of treatment were included in the present study. In the two trials, 139 patients completed 48 wk treatment with both biopsies (Figure 1). In each original trial[22-24], the patients were randomly assigned to the trial drugs.

Quantitative serum HBcrAg assay

The quantification of HBcrAg was performed using a fully automated Lumipulse chemiluminescence enzyme immunoassay analyzer (Fujirebio Inc., Tokyo, Japan) according to the manufacturer's instructions. Serum was pretreated with sodium dodecyl sulfate and incubated with monoclonal antibodies against denatured HBcAg and HBeAg. After washing and incubation with secondary antibodies, the concentrations of HBcrAg were determined by relative chemiluminescence intensity and compared with a standard curve. Because the general analytic measurement range of the assay was between 1000 U/mL (3 $\log_{10}$ U/mL) and 10000000 U/mL (7 $\log_{10}$ U/mL), serial dilutions of the serum sample were needed when the serum qHBcrAg level was above the detection limit of the assay.

Biochemistry and other indicators

Fasting venous blood was centrifuged at 4000 rpm for 10 min to obtain serum. All laboratory assessments were performed at baseline and weeks 4, 12, 24, 48, and 96.

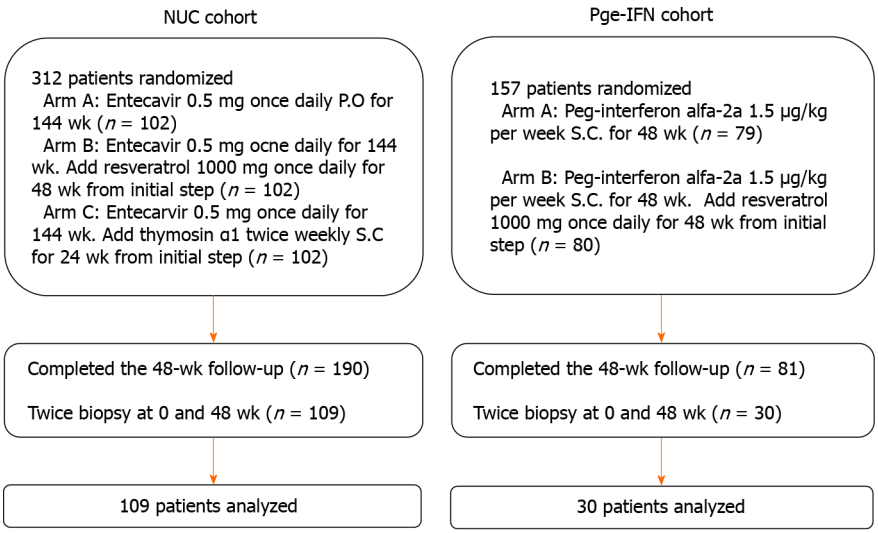


Figure 1 Patient flowchart. NUC: Nucleos(t)ide analog; Peg-IFN: Peginterferon.

HBV DNA was detected by quantitative polymerase chain reaction (PCR) using the Roche COBAS AmpliPrep/COBAS TaqMan system (Roche Diagnostics, Basel, Switzerland). The lowest detection limit was 20 IU/mL. Hepatitis B surface antigen (HBsAg), anti-HBs, HBeAg, anti-HBe, and anti-HBc were detected by chemiluminescence microparticle immunoassays using the Architect i2000SR platform and Abbott Architect reagents (Abbott Laboratories, Abbott Park, IL, United States). Serum HBsAg levels were measured with a dynamic range of 0-250 IU/mL. If qHBsAg levels were > 250 IU/mL, the samples were retested with a stepwise dilution of 1:10,000. ALT and aspartate aminotransferase were measured at each participating medical site. ALT, HBsAg, HBeAg, and HBV DNA were directly detected immediately at each time point. The HBV genotype was determined at screening. HBV pgRNA was measured at Peking University Health Science Center (Beijing, China), as previously described[25]. HBV genotypes were determined by real-time PCR with Taqman probe technology (Shanghai ZJ Bio-Tech, Shanghai, China). A FibroScan system was used to measure liver stiffness (Echosens, Paris, France).

Intrahepatic indicators

All patients in this study underwent liver biopsy before treatment and after 48 wk of treatment. The remaining liver tissue was stored in liquid nitrogen. Quantitative intrahepatic cccDNA was detected by PCR-fluorescent probing (SUPBIO Biotechnology, Beijing, China) following the manufacturer's instructions. Intrahepatic HBV DNA was detected by quantitative PCR using the Roche COBAS AmpliPrep/COBAS TaqMan system (Roche Diagnostics, Basel, Switzerland).

Statistical analyses

Continuous data were expressed as means ± SD and analyzed using Student's *t*-test or Mann-Whitney *U*-test, as appropriate based on the results of the Kolmogorov-Smirnov test. Intragroup analyses were performed using the paired ˆ-test or repeated-measure analysis of variance. Categorical variables were reported as numbers and percentages (%) and analyzed using Fisher's exact test. The correlation between two continuous variables was analyzed using Spearman's bivariate correlation, with a two-tailed significance level of $P < 0.01$. Receiver operating characteristic (ROC) curves were generated to compare the relative sensitivity and specificity of HBcrAg as a predictor of HBeAg seroconversion. A multivariable logistic regression model was used to determine whether the level of HBcrAg was a risk factor of HBeAg seroconversion. Otherwise, two-tailed *P* values of < 0.05 were considered statistically significant in all analyses. The statistical analysis were performed with SPSS 18.0 (IBM, Armonk, NY, United States).

RESULTS

Patient Characteristics

From the two original trials, 139 patients were eligible (Table 1). Among them, 69.1% were men, and 30.9% were women. There were more patients with HBV genotype C (79.9%) than B (20.1%). At baseline, the mean levels of intrahepatic HBV cccDNA were 26.65 ± 11.03 copies/cell. The mean levels of serum HBV DNA and HBsAg were 7.59 ± 1.05 $\log_{10}$ IU/mL and 3.81 ± 0.69 $\log_{10}$ IU/mL, respectively. The detailed baseline characteristics of the patients in the ETV and Peg-IFN cohorts are shown in Supplementary Table 1. The patients in the Peg-IFN cohort were younger than those in the ETV cohort (P = 0.045); there were no significant differences in the other characteristics.

Serum HBcrAg distribution

The serum qHBcrAg levels were different among the 139 patients with different phases of HBV infection and treatment. Indeed, the levels of qHBcrAg were 2.30-7.80 $\log_{10}$ U/mL. The mean levels were 5.24 ± 1.07 $\log_{10}$ U/mL in the ETV group (Figure 2A) and 5.38 ± 1.22 in the Peg-IFN group (Figure 2B) at baseline. The mean levels of qHBcrAg were 5.32 ± 1.18 $\log_{10}$ U/mL at baseline and 3.50 ± 1.31 $\log_{10}$ U/mL at week 48, showing decreases at each time point after treatment initiation (all P < 0.0001. Figure 2A-C), and there were no differences between the two groups (P = 0.6291, Figure 2D).

Comparison of the changes in qHBcrAg with other markers during treatment

Among the 139 patients, the serum qHBcrAg levels were positively correlated with cccDNA (r = 0.527, P < 0.0001; r = 0.323, P = 0.0001) and pgRNA (r = 0.597, P < 0.0001; r = 0.592, P = 0.0001) levels before and after treatment (Figure 3A and B). The correlation of serum qHBcrAg levels and intrahepatic HBV DNA levels was statistically significant at week 0 (r = 0.399, P < 0.0001, Figure 3A) and at week 48 (r = 0.213, P = 0.001) (Figure 3B). The serum qHBcrAg levels and FibroScan score weakly correlated (r = −0.278, P = 0.0099) (Supplementary Figure 1). Correlations were also observed between serum HBsAg (r = 0.514, P < 0.0001) and HBeAg (r = 0.744, P < 0.0001), but there was no significant correlation with HBcAb (r = −0.151, P = 0.0758) (Supplementary Figure 1).

Correlation between serum HBsAg and cccDNA

Serum HBsAg was weakly correlated with cccDNA levels at baseline (r = 0.265, P < 0.001) and week 48 (r = 0.141, P = 0.092; Figure 4A and B). The correlation between HBsAg and cccDNA levels at week 48 was weak in both treatment cohorts (Figure 4C and D).

Performance of HBcrAg levels for HBeAg negative conversion prediction

The levels of serum HBcrAg were significantly lower in patients with HBeAg conversion compared with those without (Figure 5A). The area under the ROC curve of HBcrAg levels for the prediction of HBeAg seroconversion was 0.643 [95% confidence interval (CI): 0.484-0.802, P = 0.072], 0.750 (95%CI: 0.629-0.872, P = 0.002), 0.794 (95%CI: 0.679-0.908, P < 0.001), and 0.825 (95%CI: 0.738-0.913, P < 0.001) at baseline, 12, 24, and 48 wk, respectively (Figure 5B). At baseline, the best cutoff of HBcrAg was 5.29 $\log_{10}$ U/mL, with 73.3% sensitivity and 66.5% specificity for predicting HBeAg seroconversion. At 12 wk, the cutoff of HBcrAg was 3.22 $\log_{10}$ U/mL, with 66.7% sensitivity and 78.2% specificity. At 24 wk, the cutoff of HBcrAg was 3.00 $\log_{10}$ U/mL, with 86.7% sensitivity and 74.8% specificity. At 48 wk, the cutoff of HBcrAg was 2.68 $\log_{10}$ U/mL, with 80.0% sensitivity and 78.6% specificity. In the multivariable model of HBeAg seroconversion, Log_{10}HBcrAg at weeks 24 and 48 was independently associated with HBeAg [odds ratio (OR) = 2.402, 95%CI: 1.314-4.391, P = 0.004; OR = 3.587, 95%CI: 1.315-9.784, P = 0.013].

DISCUSSION

qHBcrAg better represents intrahepatic levels of HBV cccDNA than HBV DNA or HBeAg[19,20,26], but data are still lacking in support of its wide clinical application. Therefore, this study aimed to investigate serum qHBcrAg levels in patients with CHB and assess the correlation of serum qHBcrAg with pgRNA and cccDNA. As expected,

Table 1 Baseline characteristics of the patients

Characteristic	*n* = 139
Age, yr, median (range)	30.4 (19-62)
Sex (male/female, %)	96/43 (69.1/30.9)
HBV genotype, *n* (%)	
B	28 (20.1)
C	111 (79.9)
ALT, U/mL, mean ± SD	174.07 ± 119.82
Serum HBV DNA, $\log_{10}$ IU/mL, mean ± SD	7.59 ± 1.05
Serum pgRNA, $\log_{10}$ copies/mL, mean ± SD	7.82 ± 1.17
ihHBV cccDNA, copies/cell	26.65 ± 11.03
ihHBV DNA, copies/cell	385.13 ± 86.09
Serum HBsAg, $\log_{10}$ IU/mL, mean ± SD	3.81 ± 0.69
Serum HBeAg, $\log_{10}$ S/CO, mean ± SD	2.49 ± 0.82
HBcrAg, $\log_{10}$ U/mL, mean ± SD	5.32 ± 1.18

ALT: Alanine transaminase; cccDNA: Covalently closed circular DNA; HBcrAg: Hepatitis B core-related antigen. HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; ihHBV: Intrahepatic hepatitis B virus.

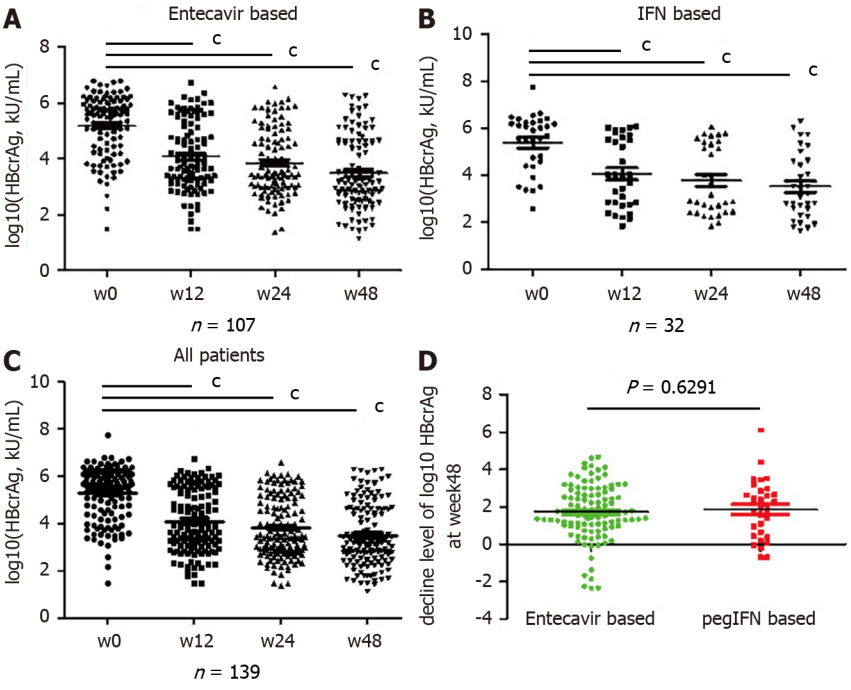


Figure 2 Time-dependent distribution of serum quantitative hepatitis B core-related antigen in patients with chronic hepatitis B and treated with different regimens. A: Changes in hepatitis B core-related antigen (HBcrAg) levels during treatment in the entecavir group; B: Changes in HBcrAg levels during treatment in the peginterferon group; C: Changes in HBcrAg levels during treatment in all patients; D: Comparison of the decrease in HBcrAg levels from baseline to week 48 between the entecavir and peginterferon groups. °P < 0.0001. HBcrAg: Hepatitis B core-related antigen; IFN: Interferon.

serum qHBcrAg was significantly and positively associated with the intrahepatic levels of cccDNA in CHB, and the association was stronger than the correlation between serum qHBsAg and intrahepatic cccDNA. Furthermore, antiviral therapy reduced the serum levels of HBcrAg and HBV DNA and the intrahepatic levels of cccDNA. The results suggest that serum HBcrAg levels correlate with HBV virological markers and could be used to predict CHB treatment outcomes, especially HBeAg seroconversion.

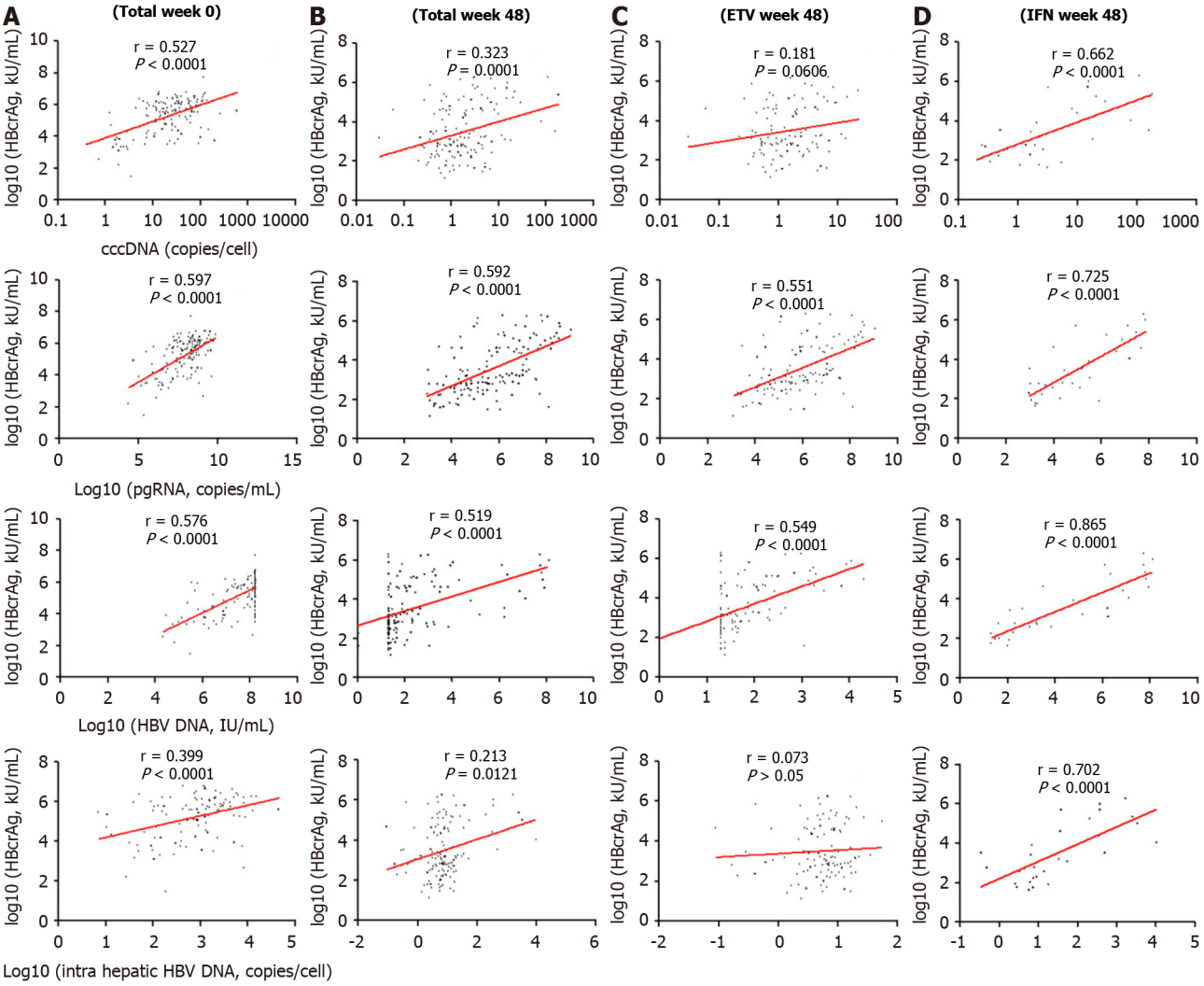


Figure 3 Correlation of serum quantitative hepatitis B core-related antigen with covalently closed circular DNA, pregenomic RNA, serum, and intrahepatic hepatitis B virus DNA level. A: In all patients at baseline; B: In all patients at week 48; C: Entecavir at week 48; D: Peginterferon at week 48. cccDNA: Covalently closed circular DNA; ETV: Entecavir; HBV: Hepatitis B virus; IFN: Interferon. pgRNA: Pregenomic RNA.

Serum levels of HBV DNA have been considered for many decades as a marker of the intrahepatic levels of cccDNA in untreated patients with CHB, but not when they are under treatment with NUCs. Indeed, under treatment, the decrease of the intrahepatic levels of cccDNA was not proportional to the steep decrease of the serum levels of HBV DNA[19,20]. Therefore, more reliable biomarkers were sought, and HBcrAg was found to be a potential additional biomarker of HBV infection, with a good correlation with intrahepatic levels of cccDNA[19,25,26]. HBcrAg was also suggested to be a reliable surrogate of cccDNA in two previous studies, as qHBcrAg was strongly correlated with intrahepatic cccDNA (r = 0.929 and 0.70, respectively), which is superior to that of qHBsAg and HBV DNA[27,28]. Hence, this study first aimed to investigate the correlation between the serum levels of qHBcrAg and the intrahepatic levels of cccDNA during CHB in Chinese patients. It showed that qHBcrAg was correlated with cccDNA before and after 48 wk of treatment, and the findings are supported by two previous studies[14,29]. HBcrAg more effectively represents cccDNA levels because HBcrAg includes three proteins: HBeAg, p22cr, and HBsAg. HBeAg is secreted by hepatocytes, p22cr represents empty virions, and HBsAg represents both empty virions and viable Dane particles[30]. Therefore, HBcrAg comprehensively encompasses the whole process of viral replication from cccDNA.

Of importance, decreases of the serum HBcrAg level were positively associated with decreases of the intrahepatic levels of cccDNA, even under therapy. Hence, the serum levels of HBcrAg could be a biomarker for the intrahepatic levels of cccDNA. In addition, because the changes in HBcrAg parallel those of intrahepatic cccDNA during treatment, it might be a better long-term prognostic indicator of CHB outcomes than

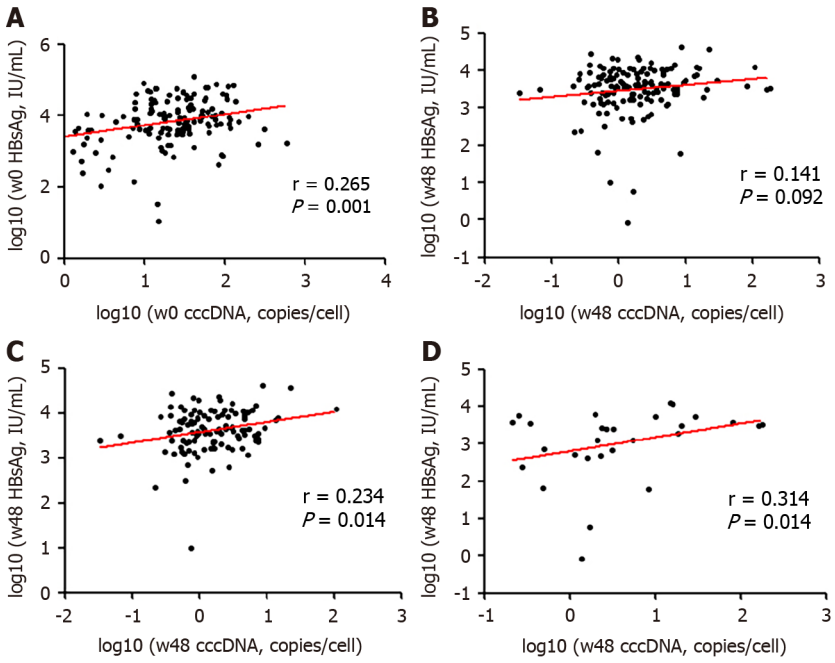
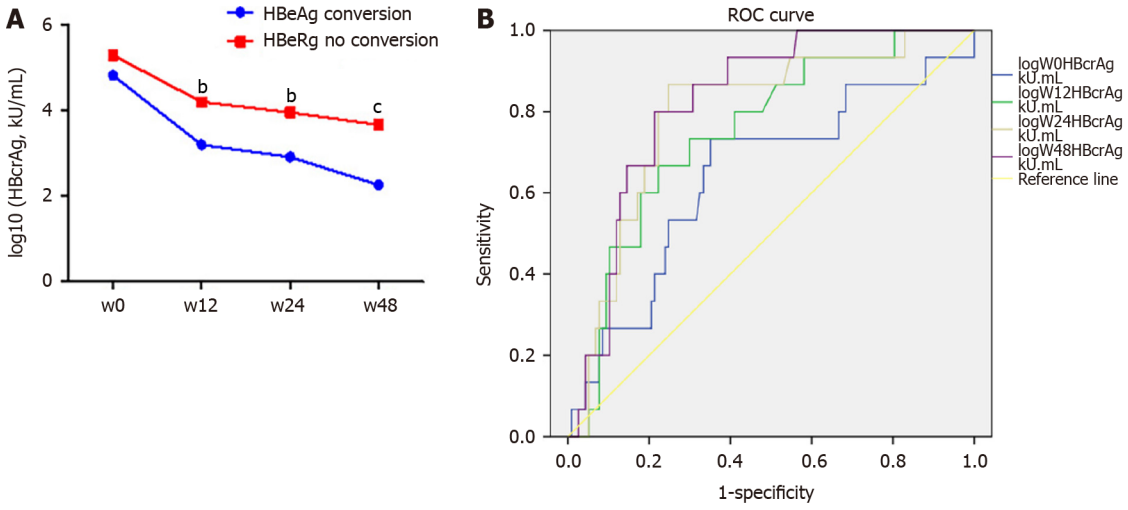


Figure 4 Correlation of serum hepatitis B surface antigen with covalently closed circular DNA. A: Correlation between serum hepatitis B surface antigen (HBsAg) and intrahepatic covalently closed circular DNA (cccDNA) at baseline; B: Correlation between serum HBsAg and intrahepatic cccDNA and at week 48; C: Correlation between cccDNA and HBsAg levels at weeks 48 in the entecavir cohort; D: Correlation between cccDNA and HBsAg levels at weeks 48 in the interferon cohort. HBsAg: Hepatitis B surface antigen; cccDNA: Covalently closed circular DNA.



			95% confidence interval	
	Area	*P* value	Lower bound	Upper bound
LogW0 HBcrAg	0.643	0.072	0.484	0.802
LogW12 HBcrAg	0.750	0.002	0.629	0.872
LogW24 HBcrAg	0.794	0.000	0.679	0.908
LogW48 HBcrAg	0.825	0.000	0.738	0.913

Figure 5 Hepatitis B core-related antigen prediction of hepatitis B e antigen seroconversion at 48 wk. A: Concentration of hepatitis B core-related antigen (HBcrAg) at different times in the two groups of hepatitis B e antigen (HBeAg) seroconversion; B: Receiver operating characteristic curve analysis of HBcrAg to predict HBeAg seroconversion. HBcrAg: Hepatitis B core-related antigen; HBeAg: Hepatitis B e antigen; ROC: Receiver operating characteristic; W: Week.

other biomarkers (*i.e.* serum HBV DNA and HBeAg). HBcrAg levels are determined by the transcription level of cccDNA. Therefore, decline of the HBcrAg levels with NUCs is slower than the decline of the serum levels of HBV DNA in patients. The slower decline might also explain why the serum levels of HBcrAg were positively correlated with the intrahepatic levels of cccDNA, either before or after ETV treatment.

In addition, the levels of serum qHBcrAg were higher in this study than in a previous study[31], which might have been the result of the high proportion of HBeAg-positive patients in this study. Considering that viral replication and host immune responses can be influenced by the HBV genotype, the distribution of the serum levels of HBcrAg was examined between patients carrying the HBV genotypes B and C, but the difference was not statistically significant. HBcrAg is a pre-core protein encoded by the pre-core/core regions of the HBV genome. Hence, the production of HBcrAg is not affected by the promoters found in the S region[18], possibly explaining the similar distribution of HBcrAg between the genotypes.

The serum levels of qHBsAg reflect the intrahepatic levels of cccDNA[19,20]. Still, in this study, the correlation between qHBsAg and intrahepatic cccDNA was weaker than the correlation between serum qHBcrAg and intrahepatic cccDNA, both without and under treatment. Most patients with HBsAg loss or seroconversion still had detectable levels of intrahepatic cccDNA and HBV DNA. Thus, according to the currently available evidence, serum levels of qHBcrAg could be more appropriate than HBsAg as a biomarker of the intrahepatic levels of cccDNA, but that needs to be confirmed in larger studies. The predictive value of qHBcrAg for HBeAg seroconversion was the best at 24 and 48 wk. That could be because baseline qHBcrAg is not predictive of the response to treatment, and that 12 wk is too early to observe a proper response. Additional studies are necessary to determine the best timing of qHBcrAg measurement for the prognosis of CHB. Nevertheless, qHBcrAg levels at the other time points were still associated with HBeAg seroconversion, as observed in previous studies[32-35]. HBsAg and HBeAg each represent only a part of the process of HBV production and assembly, and that could explain why they have a lower prognostic value, especially HBsAg at 48 wk[30].

The study has limitations. It was a secondary analysis of patients from two different trials with two different antiviral treatments and different regimens. Not all patients underwent two biopsies, leading to a selection bias and a small sample size. Importantly, a biopsy was performed at 48 wk in both studies. Still, the patients were followed for up to 144 wk in the ETV group and 96 wk in the Peg-IFN group, but the patients were only treated with Peg-IFN for 48 wk, and the long-term changes in HBcrAg are unknown. HBV genotype D is very rare in China and was not included in the two trials. Therefore, future studies should address those points.

CONCLUSION

Serum qHBcrAg levels were correlated with the intrahepatic levels of cccDNA in patients with CHB and might be an acceptable surrogate marker for cccDNA. HBcrAg levels correlated with HBV virological markers and could be used to predict CHB treatment outcomes, especially HBeAg seroconversion. Hence, serum qHBcrAg might be used in the clinical setting for monitoring intrahepatic HBV status and determining the long-term prognosis of patients with CHB.

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ARTICLE HIGHLIGHTS

Research background

Quantitative hepatitis B core-related antigen (qHBcrAg) had a better correlation with intrahepatic hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) than either HBV DNA or hepatitis B e antigen (HBeAg).

Research motivation

Data are still lacking for the widespread clinical application of qHBcrAg.

Research objectives

This study aimed to investigate the serum qHBcrAg levels in patients with chronic hepatitis B (CHB) and to assess the correlation of serum qHBcrAg with pregenomic RNA (pgRNA), cccDNA, and HBeAg seroconversion.

Research methods

This was a secondary analysis of patients who underwent percutaneous liver biopsy in two multicenter, randomized, controlled clinical trials. Serum qHBcrAg, pgRNA, HBV DNA, hepatitis B core antigen, and HBeAg and liver cccDNA, and HBV DNA were measured. The correlations of serum qHBcrAg with other biomarkers were tested.

Research results

Serum qHBcrAg levels were positively associated with pgRNA ($r = 0.597$, $P < 0.0001$) and cccDNA ($r = 0.527$, $P < 0.0001$) levels. HBcrAg predicted HBeAg seroconversion, with an area under the receiver operating characteristics curve of 0.788 at 24 wk and 0.825 at 48 wk.

Research conclusions

Serum HBcrAg levels correlated with HBV virological markers and could be used to predict HBeAg seroconversion.

Research perspectives

Serum qHBcrAg might be used in the clinical setting to monitor intrahepatic HBV status and determine the long-term prognosis of patients with CHB.

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