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HCV core antigen is a useful predictor during pegylated-interferon/ribavirin therapy in patients with hepatitis C virus genotype 1b

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Abstract

Enzyme immunoassays for quantifying hepatitis C virus (HCV) core antigen (Ag) have been proposed as an alternative to HCV RNA detection. The present study aimed to investigate the early kinetics of serum HCVcAg and its usefulness in predicting virological responses.

The clinical data of 135 patients with chronic hepatitis C treated with pegylated interferon alpha (PEG-IFN-α) and ribavirin was retrospectively collected. The patients were grouped according to their treatment outcomes as follows: sustained virological response (SVR), nonsustained virological response (N-SVR), and relapse.

Higher HCVcAg and HCV RNA levels were observed in patients in the N-SVR group than in the other groups at baseline. HCVcAg better predicted rapid virological response (RVR) compared with HCV RNA and had a predictive value similar to that of HCV RNA for SVR and early virological response. In the relapse group, HCV RNA decreased to 0 after 48 weeks, whereas HCVcAg was still detectable, indicating that HCVcAg more sensitively predicted relapse in antiviral therapy than HCV RNA.

For patients treated with PEG-INF-α and ribavirin, HCVcAg may more sensitively predict relapse than HCV RNA.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, AUROC = area under the univariate receiver operating characteristic, CHC = chronic hepatitis C, EVR = early virological response, HCV = hepatitis C virus, HCVcAg = HCV core antigen, N-SVR = nonsustained virological response, PCR = polymerase chain reaction, PEG-IFN = pegylated interferon, RVR = rapid virological response, SVR = sustained virological response.

Keywords: chronic hepatitis C, hepatitis C virus core antigen, hepatitis C virus RNA, relapse, sustained virological response

1. Introduction

Chronic hepatitis C virus (HCV) infection results in progressive disease and afflicts more than 185 million people worldwide.[1] Progression of hepatic fibrosis, cirrhosis, or carcinoma is consistently observed in patients with chronic HCV infection.[2] Treatment and monitoring of HCV infection are a great challenge for many countries, especially in developing countries. In China, HCV genotype 1b accounts for 70% of all cases of HCV infection.[3] Treatment of HCV genotype 1 has evolved from pegylated interferon (PEG-IFN) and ribavirin to direct-acting antiviral agents. In recent years, new treatments for chronic infection with HCV genotype 1b have emerged, such as the combination of simeprevir and sofosbuvir[4] and that of ledipasvir and sofosbuvir.[5] Although the treatment response of chronic hepatitis C (CHC) has been improved with combination antiviral drug therapy, about 50% of patients with CHC genotype 1b do not achieve sustained virological response (SVR). In addition, the high cost of treatment and adverse effects often lead to treatment failure.[6] Therefore, a predictive indicator would enable prompt treatment when adverse effects occur.

HCV RNA quantification has been used to assess early virological response (EVR) in the treatment of chronic HCV infection owing to its high sensitivity (detection limit as low as 50 IU/mL), high specificity, and reproducibility. However, the high cost associated with this assay hinders its use in resource-limited settings.[7] In addition, like other molecular assays typically performed in batches, HCV RNA quantification lacks a short turn-around time, delaying clinical decision-making.[8]

The CE-marked HCV core antigen (HCVcAg) quantification assay (ARCHITECT HCV Ag assay; Abbott Diagnostics, Wiesbaden, Germany) is a rapid, affordable, and simplified method.[9] Many studies have found a correlation between the levels of serum HCVcAg and HCV RNA in patients with CHC.[10–15] Recently, serum HCVcAg levels have been reported to predict early SVR in patients with HCV genotype 1b.[16,17] However, it is not clear whether HCVcAg levels can predict SVR and relapse in Chinese patients infected with HCV genotype 1b.

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The present study aimed to compare the levels of HCVcAg, HCV RNA, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) between patients with different treatment outcomes: SVR, nonsustained virological response (N-SVR), and relapse (positive after 24 weeks of treatment). In addition, the predictive roles of HCVcAg at different phases of HCV genotype 1b infection treatment were explored.

2. Materials and methods

2.1. Patients

The clinical data of 135 patients (65 men and 70 women) treated with PEG-IFN-α and ribavirin for HCV genotype 1b infection were retrospectively collected. This study was approved by the Tianjin Third Central Hospital Ethics Committee (Approval Number: IRB2014-019-02). Patients with the following conditions were excluded: liver dysfunction, pregnancy, major diseases, amentia, neutrophil count $<1.5\times10^9$/L, white blood cell counts $<3\times10^9$/L, and platelet counts $<90\times10^9$/L.

2.2. Treatment protocol

Patients were treated with PEG-IFN-α (Peg-Intron; Schering-Plough, Kenilworth, NJ; 180 μg/wk for body weight ≥65 kg and 135 μg/wk for body weight <65 kg) in combination with ribavirin (Rebetol; Schering-Plough; 1000 mg/d for body weight ≥65 kg and 800 mg/d for body weight <65 kg). After the initial 12-week treatment, if the HCV RNA level decreased at least by 2 $\log_{10}$ or the patient was HCV RNA negative, the treatment was continued for another 36 weeks; otherwise, treatment was discontinued.

2.3. Virological and serological testing

HCV RNA levels were measured at 0, 4, 12, 24, 36, 48, and 72 weeks of treatment using real-time polymerase chain reaction (PCR) with a lower limit of detection of 43 IU/mL (COBAS AmpliPrep/COBAS TaqMan, Roche Molecular Systems, Pleasanton, CA). HCVcAg levels were measured using chemiluminescent microparticle immunoassay (ARCHITECT HCVcAg system, Abbott Diagnostics). HCVcAg levels <3.0 fM were considered nonreactive. One $\log_{10}$ reduction of serum HCVcAg levels was defined as dHCVcAg. HCV genotyping was performed using real-time fluorescence-based quantitative PCR (ABI ViiA 7, Thermo Fisher Scientific, Massachusetts). Anti-HCV antibodies were detected using enzyme-linked immunosorbent assay, and positivity was confirmed when both the tests were positive (S/cutoff >1). ALT and AST levels were measured using enzyme-catalyzed reactions (TBA-2000FR, Toshiba, Tokyo, Japan).

2.4. Definition of response

The lower limit of HCV RNA detection was 50 IU/mL in our study. An undetectable HCV RNA level at 24 weeks was defined as SVR. An undetectable HCV RNA level starting from 4 weeks until the end of treatment was defined as a rapid virological response (RVR).[18] A detectable HCV RNA level at the end of treatment was defined as N-SVR. Undetectable HCV RNA at the end of treatment and detectable HCV RNA 24 weeks later indicated relapse.

2.5. Statistical analysis

All statistical analyses were performed with SPSS Statistics 20.0 (Chicago, IL). Continuous data are presented as means ± standard deviations. The parallel normality and homogeneity of variance tests were both examined. Data with non-normal distributions were processed using natural logarithmic transformation before statistical analysis. Comparison between 2 groups was performed using *t* tests, and comparisons among multiple groups were performed using analysis of variance. HCV RNA loading capacity and quantitative HCVcAg were both converted to $\log_{10}$ values before statistical analysis. Comparisons of categorical data were performed using the χ^2 test. Pearson method was used to analyze the correlation of continuous variables. $P < .05$ was considered statistically significant.

Area under the univariate receiver operating characteristic (AUROC) curve was used to calculate the optimal predictive values of dHCVcAg and HCVcAg at different time points. The reliability of predictors of treatment response was assessed by sensitivity, positive and negative predictive value (PPV and NPV), and specificity.

3. Results

3.1. Baseline characteristics of patients

A total of 135 patients (age range, 29–70 years; average, 50.3 years) infected with HCV genotype 1b were included. The mean viral load was 6.12 ± 1.20 $\log_{10}$ IU/mL, and the HCV antigen level was 5.00 ± 1.19 $\log_{10}$ fM at baseline. Patients were categorized according to treatment outcome: SVR, relapse (positive after 24 weeks of treatment), and N-SVR. The baseline characteristics of these patients are shown in Table 1. Compared with patients in the SVR group, patients in the N-SVR group were older and showed significantly higher levels of HCVcAg and HCV RNA and significantly lower levels of ALT and AST at baseline. Patients in the N-SVR group were significantly older and showed significantly higher levels of HCVcAg and HCV RNA at baseline, in comparison with patients in the relapse group. No significant difference in parameters, except HCVcAg between the SVR and relapse groups, was observed at baseline. The baseline HCVcAg levels were significantly correlated with levels of HCV RNA ($r=0.986$, $P=.001$), ALT ($r=0.416$, $P=.001$), AST ($r=0.453$, $P=.001$), and AST/ALT ($r=0.201$, $P=.001$).

3.2. Influence of baseline parameters on treatment outcome

To determine the factors that correlated with different disease phases in patients with HCV genotype 1b, 7 variables—gender, HCV genotype, age, ALT level, AST level, HCV RNA, and HCVcAg—were analyzed. Regression analysis showed that

Table 1

Baseline patient characteristics.

	SVR (n = 90)	Relapse (n = 20)	N-SVR (n = 25)	*P*
Male	42	11	12	.001
Age, yr	48.73 ± 10.90	49.56 ± 12.01	53.83 ± 9.76	.004
HCVcAg, $\log_{10}$ fM	4.53 ± 0.92	5.74 ± 0.50	6.43 ± 0.99	.001
HCV RNA, $\log_{10}$ IU/mL	5.73 ± 1.04	5.87 ± 2.00	7.46 ± 0.96	.001
ALT, U/L	112.02 ± 45.24	79.01 ± 44.32	68.39 ± 39.50	.001
AST, U/L	93.18 ± 43.05	65.37 ± 35.06	33.73 ± 6.74	.001

ALT = alanine aminotransferase, AST = aspartate aminotransferase, HCVcAg = hepatitis C virus core antigen, N-SVR = nonsustained virologic response, SVR = sustained virologic response.

Table 2

Multivariate logistic regression analysis of the association between RVR and influential factors in patients with CHC.

Variables	Coefficient	χ^2	OR (95% CI)	P
HCV RNA, $\log_{10}$ copies/mL	−0.138	0.087	0.871 (0.326–2.324)	.782
HCVcAg, log10 fM	3.666	41.638	39.102 (7.085–215.788)	.001
ALT, U/L	−0.063	0.764	0.939 (0.802–1.101)	.439
AST, U/L	0.047	0.374	1.048 (0.891–1.232)	.572
Age, yr	−0.085	6.355	0.918 (0.743–14.182)	.118

CHC = chronic hepatitis C, CI = confidence interval, HCV = hepatitis C virus, OR = odds ratio, RVR = rapid virologic response, RNA = ribonucleic acid.

Table 3

Multivariate logistic regression analysis of the association between EVR and influential factors in patients with CHC.

Variables	Coefficient	χ^2	OR (95% CI)	P
HCV RNA, $\log_{10}$ copies/mL	−0.460	1.913	0.632 (0.306–1.305)	.014
HCVcAg, $\log_{10}$ fM	3.206	43.489	24.682 (6.116–99.612)	.001
ALT, U/L	−0.019	0.288	0.981 (0.914–1.053)	.596
AST, U/L	0.014	0.130	1.014 (0.940–1.094)	.720
Age, yr	−0.042	4.860	0.959 (0.835–9.914)	.046

CHC = chronic hepatitis C, CI = confidence interval, HCV = hepatitis C virus, OR = odds ratio, RVR = rapid virologic response, RNA = ribonucleic acid.

HCVcAg was an independent factor correlated with RVR, and HCV RNA, HCVcAg, and age were associated with EVR and SVR. HCVcAg more sensitively predicted RVR than HCV RNA and had a predictive capability similar to that of HCV RNA for EVR and SVR (Tables 2–4).

3.3. Kinetics of HCVcAg and HCV RNA

The dynamic changes in serum HCVcAg and HCV RNA were used to investigate their predictive values at different time points. The kinetics of serum HCVcAg and HCV RNA showed similar values in the SVR and N-SVR groups during the 72 weeks after treatment initiation but varied in patients after relapse (Fig. 1 and Table 5). Among the 3 groups, the decline in serum HCVcAg and HCV RNA in the SVR group was the most rapid, whereas that in the N-SVR group was the slowest. At 48 weeks, the value of HCV RNA decreased to 0 in the relapse group, whereas the value of HCVcAg was still above 0. Thus, HCVcAg might more sensitively predict relapse after antiviral therapy than HCV RNA.

3.4. ROC curves of HCVcAg and HCV RNA levels for prediction of SVR

The predictive values of HCVcAg and HCV RNA within the first 12 weeks of SVR were assessed by ROC curves (Fig. 2). According to the curves, some important parameters such as PPV, sensitivity, NPV, and specificity were measured (Table 6). The AUROC curve of dHCVcAg, dHCV RNA, HCVcAg, and HCV RNA was 0.795, 0.712, 0.897, and 0.812, respectively, at 4 weeks and 0.804, 0.938, 0.912, and 0.923, respectively, at 12 weeks. In addition, at 12 weeks, the AUROC curve for HCVcAg levels was the highest at 2.23 with a cutoff of 0.912. Related sensitivity, specificity, PPV, and NPV were 96.5%, 79.5%, 91.2%, and 91.2%, respectively; PPVs of HCVcAg and HCV RNA (91.2% and 97.1%, respectively) were similar across time points.

4. Discussion

To date, many methods including detection of specific antibody for HCV, HCV RNA, or HCVcAg and HCV genotyping have been used in the diagnosis, detection, and management of HCV infection.[19,20] Quantitative detection of HCVcAg and HCV RNA levels represents the 2 mainstay methods used for the management of patients with HCV infection.[21] However, owing to the high cost, time consumption, and requirement of dedicated laboratory area, large-scale detection of HCV RNA in many laboratories of developing countries is restricted.[22] Thus, HCVcAg quantification has been increasingly considered as a surrogate marker of CHC. Considering the differences in HCV pathogenesis, morbidity, and genotypes between Asian populations and European/American populations, HCVcAg assays could represent a more cost-effective method compared with HCV RNA quantification. However, HCVcAg testing has not been considered a gold standard for diagnosing and treating

Table 4

Multivariate logistic regression analysis of the association between SVR and influential factors in patients with CHC.

Variables	Coefficient	χ^2	OR (95% CI)	P
HCV RNA, $\log_{10}$ copies/mL	−0.390	1.226	0.677 (0.326–1.405)	.025
HCVcAg, $\log_{10}$ fM	3.585	16.421	36.054 (2.38–546.158)	.01
ALT, U/L	−0.099	2.897	0.906 (0.794–1.033)	.141
AST, U/L	0.088	1.949	1.093 (0.951–1.255)	.211
Age, yr	−0.076	8.169	0.927 (0.868–0.990)	.024

CHC = chronic hepatitis C, CI = confidence interval, HCV = hepatitis C virus, OR = odds ratio, RVR = rapid virologic response, RNA = ribonucleic acid.

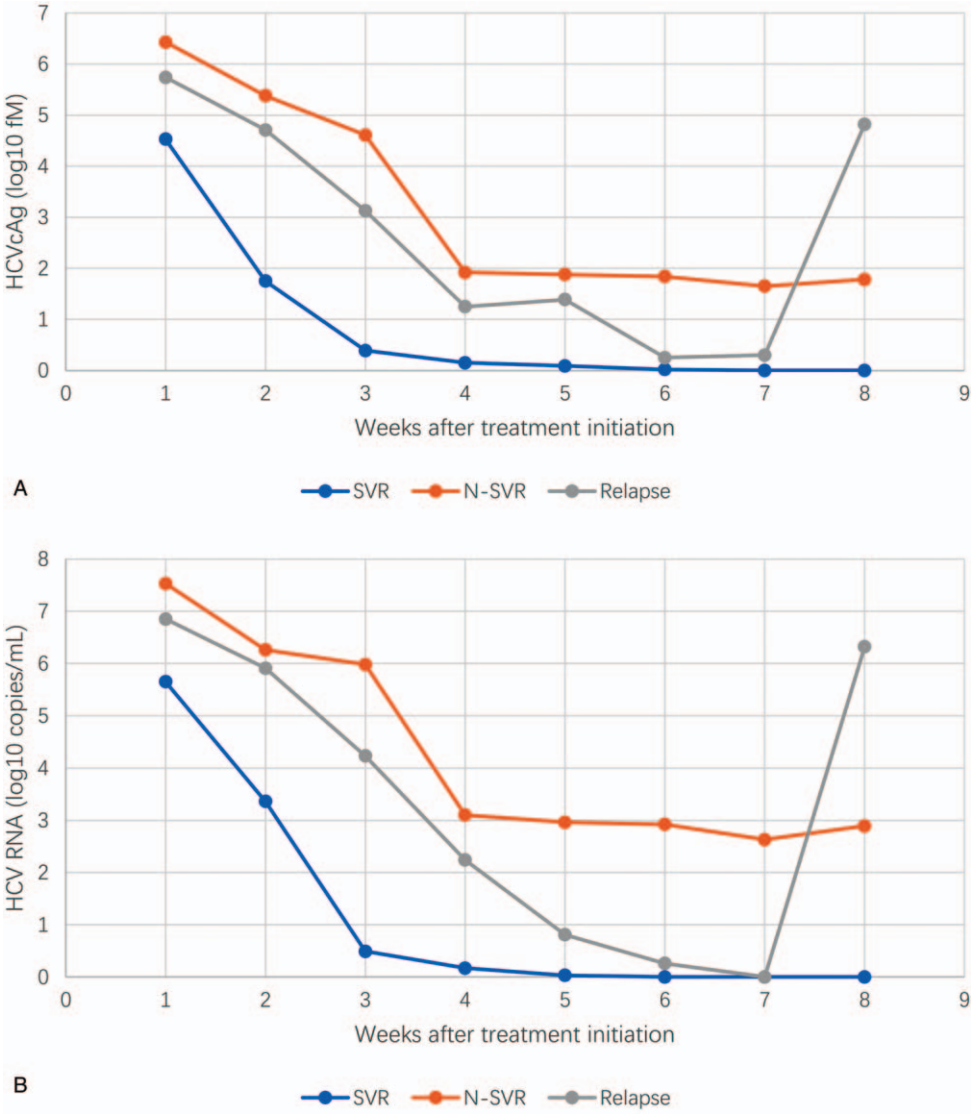

Figure 1. Dynamic changes in serum HCVcAg (A) and HCV RNA (B) levels during antiviral treatment in different groups of patients. HCV = hepatitis C virus, HCVcAg = HCV core antigen, RNA = ribonucleic acid.

Table 5

HCVcAg and HCV RNA levels at different time points during treatment.

	HCVcAg, log_{10} fM			HCV RNA, log_{10} copies/mL		
Weeks	**SVR**	**N-SVR**	**Relapse**	**SVR**	**N-SVR**	**Relapse**
0	4.53	6.43	5.74	5.65	7.53	6.85
4	1.75	5.38	4.71	3.36	6.26	5.91
12	0.39	4.61	3.13	0.49	5.98	4.23
16	0.15	1.92	1.25	0.17	3.1	2.24
20	0.09	1.88	1.39	0.03	2.96	0.81
24	0.02	1.84	0.25	0	2.92	0.26
48	0	1.65	0.3	0	2.63	0
72	0	1.78	4.82	0	2.89	6.32

HCV = hepatitis C virus, HCVcAg = HCV core antigen, N-SVR = nonsustained virological response, RNA = ribonucleic acid, SVR = sustained virological response.

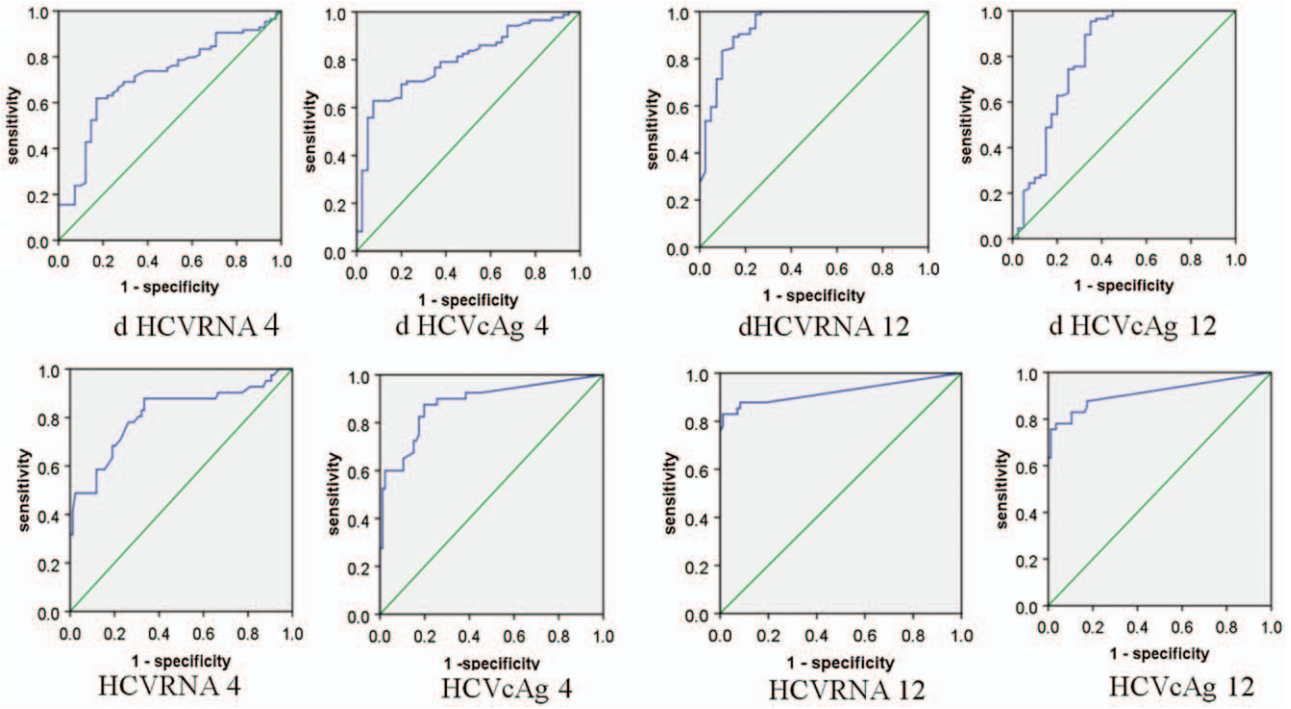

Figure 2. ROC curves of HCVcAg and HCV RNA levels at weeks 4 and 12 to predict SVR. AUROC curve was calculated to compare the values of HCVcAg and HCV RNA at weeks 4 and 12 to predict SVR and identify the optimal cutoff values. The random classifier line indicates a 50% post-test probability, and the cutoff point represents the best compromise between sensitivity and specificity for the 2 assays. AUROC = area under the univariate receiver operating characteristic, SVR = sustained virological response.

HCV infection in China.[23] Its clinical utility remains to be proven in large clinical trials.

In the present study, the correlation between HCV RNA and HCVcAg levels was analyzed using bivariate association analysis. Our study found a significant positive correlation between HCVcAg level and HCV RNA load but a low correlation between HCVcAg levels and ALT and AST levels, consistent with previous studies.[24–26] For example, in comparison of different HCV RNA kits and the HCVcAg test, Medici et al[24] revealed a correlation coefficient ranging from 0.713 to 0.870.

Recently, many studies have focused on the relevance of HCVcAg kinetics in the early prediction of SVR.[15–17,27] However, only a few studies have investigated the difference between the HCVcAg test and HCV RNA test in predicting SVR, EVR, RVR, and relapse in patients treated with PEG-IFN and ribavirin for HCV genotype 1b infection. Our study used multivariate logistic regression analysis to reveal the association between influencing factors and the different outcomes of HCV genotype 1b infection treatment (EVR, RVR, and SVR).

An important finding of the present study was that HCVcAg and HCV RNA predicted EVR and SVR similarly, whereas for RVR, HCVcAg was a better predictor than HCV RNA, as HCVcAg was the only independent factor associated with RVR. Moreover, the dynamic changes in serum HCV RNA and HCVcAg in the 3 groups—SVR, N-SVR, and relapse—were tested. We found that during the 72 weeks after treatment initiation, kinetics of serum HCVcAg and HCV RNA showed similar values in the SVR, relapse, and N-SVR groups but varied in patients after relapse. This was consistent with previous findings that serum HCV RNA is undetectable in approximately

Table 6

Area under the ROC curve, sensitivity, specificity, and predictive values of the SVR based on total HCVcAg and HCV RNA levels at 4 and 12 weeks after treatment initiation.

	dHCVcAg4	dHCVRNA4	HCVcAg4	HCVRNA4	dHCVcAg12	dHCVRNA12	HCVcAg12	HCVRNA12
ROC	0.795	0.712	0.897	0.812	0.804	0.938	0.912	0.923
(95% CI)	(0.708–0.857)	(0.624–0.790)	(0.830–0.944)	(0.733–0.877)	(0.724–0.870)	(0.880–0.970)	(0.848–0.978)	(0.861–0.963)
Cutoff	2.02	1.92	3.76	4.56	2.93	3.68	2.23	3.5
Sensitivity	0.623	0.829	0.802	0.878	0.954	0.854	0.965	0.829
Specificity	0.923	0.619	0.897	0.667	0.641	0.893	0.795	0.988
PPV	0.947	0.515	0.975	0.562	0.854	0.795	0.912	0.971
NPV	0.529	0.881	0.673	0.918	0.862	0.926	0.912	0.922

All data are presented as $\log_{10}$ values, and dHCVcAg and dHCVRNA were defined as a $\log_{10}$ reduction of serum HCVcAg and HCV RNA levels between other time points and baseline, respectively.
AUROC = area under the univariate receiver operating characteristic curve, CI = confidence interval, HCVcAg = hepatitis C virus core antigen, NPV = negative predictive value, PPV = positive predictive value, RNA = ribonucleic acid.

50% of patients after IFN-based treatment for chronic HCV infection, thereby resulting in high rates of relapse.[28]

Among the 3 groups, the decline in serum HCVcAg and HCV RNA in the SVR group was the most rapid, whereas that in the N-SVR group was the slowest. This result indicated that anti-HCV treatment outcomes can be predicted by HCVcAg determination. Interestingly, in the relapse group, the value of HCV RNA decreased to 0, whereas the value of HCVcAg remained above 0 at 48 weeks, suggesting that HCVcAg might be a more sensitive predictor of relapse after antiviral therapy compared with HCV RNA. We also assessed the best SVR predictive cutoffs of HCVcAg, dHCVcAg, HCV RNA, and dHCV RNA by calculating the AUROC curve at weeks 4 and 12. The results showed that at the same time points, the AUROC curve of HCVcAg or dHCVcAg was smaller than that of HCV RNA or dHCV RNA. The highest AUROC curve of 0.912 was obtained for HCVcAg levels, with a cutoff value of 2.23 at 12 weeks. The cutoff value yields of PPV and NPV were 91.2% and 91.2%, respectively. At the same time, compared with those of HCV RNA, the PPV and NPV of HCVcAg showed a smaller decline (91.2% and 97.1%). In addition, HCVcAg showed higher sensitivity than HCV RNA, indicating that HCVcAg is a more sensitive predictor of SVR in the treatment of HCV infection.

Our study had some limitations. First, the retrospective design may have introduced selection bias. Second, no randomization was performed in our study, and thus uncontrolled factors may have influenced the results. Third, the follow-up time was relatively short.

In conclusion, there was a strong correlation between HCV RNA and HCVcAg concentrations in individuals with HCV genotype 1b infection. In patients with CHC treated with PEG-IFN and ribavirin, serum HCVcAg had the same predictive efficacy for SVR and EVR as HCV RNA. Although HCVcAg and dHCVcAg had lower AUROC curve than HCV RNA and dHCV RNA, the sensitivity of the HCVcAg test was higher than that of HCV RNA, which implies that HCVcAg may have the same efficacy as HCV RNA in predicting SVR. We found that serum levels of HCVcAg were associated with RVR and relapse and might predict these events after antiviral therapy with higher sensitivity than HCV RNA. Thus, HCVcAg testing may represent an alternative approach to conventional HCV RNA quantification, with the advantages of speed, reproducibility, and reliability in settings with limited resources. Furthermore, HCVcAg could be a better independent factor for predicting RVR and relapse. In addition, combined analysis of HCVcAg and HCV RNA may be applied in clinical monitoring of CHC.

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