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RESEARCH ARTICLE

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The correlation of HCV RNA and HCV core antigen in different genotypes of HCV

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Background: To analyze the correlation of HCV RNA and HCV core antigen (HCV cAg) in different genotypes of HCV.
Methods: One hundred and six patients who were diagnosed with HCV infection by HCV RNA test were included in the study. HCV genotypes were detected by PCR fluorescent probe. Detected HCV cAg's expression in serum quantitatively and qualitatively with chemiluminescent micro-particle immuno assay (CMIA) and enzyme-linked immunosorbent assay (ELISA), respectively, and compared positive rates. Analyzed the correlation of HCV RNA and HCV cAg in different genotypes.
Results: Distribution of HCV genotypes in 106 HCV infected patients were as follows: 1b genotype 46 (43.4%); 2a genotype 7 (6.6%); 3a genotype 18 (17.0%); 3b genotype 3 (2.8%); 6a genotype 9 (8.5%); 1b/3b mixed type 13 (12.3%); and unidentified type 10 (9.4%). Positive rates of HCV cAg detected by CMIA and ELISA were 100% and 56%, respectively, with statistical significance ($\chi^2 = 60.38$, $P = 0.000$). HCV cAg in 1b genotype group was higher than that in 3b and 1b/3b genotype groups, with statistical significance ($U = 3.0$, $P = 0.006$, $U = 165$, $P = 0.014$). HCV RNA and HCV cAg in genotype 1b demonstrated a positive correlation ($r = 0.894$, $P = 0.04$).
Conclusion: Major genetic subtype of HCV genotype was 1b. Compared with ELISA, detection of HCV cAg by CMIA increased the positive rate and facilitated early diagnosis and treatment of HCV-infected patients. With the increase in HCV RNA load and the expression of HCV cAg, HCV cAg could be an early indicator for the diagnosis of HCV infection in 1b genotype.

KEYWORDS
correlation, genotype, HCV core antigen, HCV RNA, hepatitis C virus

1 | INTRODUCTION

Hepatitis C virus (HCV) infections are globally distributed, the total global HCV prevalence is estimated at 2.5% (177.5 million of HCV infected adults), ranging from 2.9% in Africa and 1.3% in Americas (2.8% in East Asia, including only China and Taiwan); with a global viraemic rate of 67% (118.9 million of HCV RNA-positive cases), varying from 64.4% in Asia to 74.8% in Australasia (63.6% in East Asia), HCV prevalence in China is 1.3%.[1] Without proper antiviral treatment, 20%-30% of HCV-infected patients will develop cirrhosis after 10-20 years, and 2%-7% will have primary liver cancer.[2] Hepatocellular carcinoma (HCC) is one of the most

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prevalent primary malignant tumors and accounts for about 90% of all primary liver cancers. HBV is the main causative agent in the high incidence HCC areas, HCV is the major etiological factor in low incidence HCC areas, like Western Europe and North America.[3] The rate of HCC progression varies greatly among patients with chronic HCV infection, and this is probably due to the existence of a complex interplay between host, viral, and environmental factors.[4]

At present, the positive rate of HCV cAg in serum qualitatively tested by ELISA is low and its sensitivity is lower than HCV RNA's. To improve the positive rate of HCV cAg in the diagnosis of hepatitis C, Abbott Laboratories (USA) developed the CMIA for quantitative detection of HCV cAg in 2010, with good specificity (≥99.5%) and high sensitivity (97.8%). The study intended to use CMIA quantitative test and ELISA qualitative test to detect the expression of HCV cAg in serum of HCV infected patients and to compare the positive rates of HCV cAg detected by two methods.

The antibodies to HCV (anti-HCV) are at present the most commonly available marker of HCV infection, but the most important indicator of HCV diffusion seems to be its classification into different genetic variants.[1] At present, the antiviral therapies of HCV infection still remain partially dependent on HCV genotype. There were six genotypes according to HCV genetic variability. HCV genotype 1 is the most prevalent worldwide (49.1%), followed by genotype 3 (17.9%), 4 (16.8%), and 2 (11.0%). Genotypes 5 and 6 are responsible for the remaining <5%. The predominant genotypes in East Asia are genotype 1 (53.5%) and genotype 2 (31.7%). Only a small percentage of genotype 3 and genotype 6 (5.4% and 3.3%, respectively) have been found.[1] HCV-infected patients in mainland China covered all the six genotypes.[5] The main prevalent subgenotype was 1b, followed by 2a. HCV RNA was correlated with HCV cAg without consideration of HCV genotype.[6-8] The HCV RNA expression level reflected that viral replication activity was closely related to liver inflammation degree, prognosis, and antiviral treatment.[9] As the best supplementary indicator for HCV antibody detection, HCV cAg could be a diagnostic indicator for early HCV infection. HCV cAg was detectable for 12-70 days after HCV infection. After 70 days, HCV cAg disappeared and HCV antibody was produced. The study was aimed at determining whether HCV cAg can be an early indicator for supplementary diagnosis of HCV infection by analyzing the correlation between HCV RNA load and HCV cAg of different HCV genotypes.

2 | MATERIALS AND METHODS

2.1 | Study subjects

A total of 106 patients who were diagnosed with HCV infection by HCV RNA (real-time PCR), including 63 males (59.4%) and 43 (40.6%) females with a mean age of 40 years (18-78 years) in the First Affiliated Hospital of Chongqing Medical University from May 2016 to May 2017 were enrolled into the present study. Separated serum within 12 h and stored them at −70°C. All the cases met the diagnostic criteria of *the Guideline of Prevention and Treatment for Hepatitis C* revised in 2014 by Hepatology Society and Infectious Diseases Society of Chinese Medical Association. All the patients did not contain the following conditions: acute hepatitis, HBV or HDV co-infection, pregnancy, breastfeeding, hepatocellular carcinoma, decompensated liver disease, organ transplant, hyperthyroidism, diabetes mellitus, mental illness, and HIV co-infection.

2.2 | Methods

2.2.1 | HCV RNA test

The HCV RNA load was measured by the real-time PCR (CobasZ-480 Real-time Fluorescence Quantitative PCR Instrument, Roche Pharmaceuticals Ltd., Branchburg, NJ, USA) according to the specification of HCV RNA Diagnostic Kit (Shanghai Kehua Bio-engineering Co., Ltd, Shanghai, China). The detection limit of HCV RNA assay is 250 IU/mL. The range of linearity of HCV RNA assay is 10^3-10^7.

2.2.2 | HCV genotype test

HCV genotypes of HCV infected patients were tested by the PCR fluorescent probe (CobasZ-480 Real-time Fluorescence Quantitative PCR Instrument, Roche Pharmaceuticals Ltd., USA) with specification of HCV Genotyping Diagnostic Kit (Triplex International Biosciences Co., Ltd, Xiamen, China), and five subgenotypes were detected: 1b, 2a, 3a, 3b and 6a.

2.2.3 | HCV cAg qualitative test

The ELISA was used in the test according to specification of HCV Core Antigen Diagnostic Kit (Shandong Laibo Bio-chemical Co. Ltd., Jinan City, China). Measured the OD value of each sample with TECAN Microplate Reader (Austria) to test HCV cAg (dual-wavelength was 450 nm/630-690 nm, Cut-off value=0.12).

2.2.4 | HCV cAg quantitative test

HCV cAg was tested by CMIA according to specifications of HCV Core Antigen Diagnostic Kit (Abbott Laboratories, Chicago, IL, USA) and i2000 Automatic Chemiluminescence Analyzer (Abbott Laboratories, USA). When the sample concentration ≥3.00 fmol/L, the sample was considered to be reactive in the detection of HCV cAg. The specificity of HCV Ag assay is ≥99.5%, and the sensitivity is 97.8%.

2.3 | Statistical analysis

Continuous variables were summarized as median (the inter-quartile range):M(P25,P75) and categorical variables as frequency (percentage).

Comparisons between groups were performed using the Kruskal-Wallis *H* test for continuous variables, and the χ^2 test for categorical data. Spearman's rank correlation was used for correlation analysis. Comparisons between different groups were performed using analysis of variance. All *P* values were based on a two-sided test of statistical significance. Significance was accepted at $P < 0.05$. All analyses were performed with SPSS software for windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | General clinical characteristics

Among 106 HCV-infected patients, the levels of HCV RNA, HCV cAg, ALT, and AST were expressed as medians (the inter-quartile range): M(P25,P75), shown as in Table 1.

3.2 | HCV genotype distribution

Genotype distributions of 106 HCV infected patients were as follows: 1b genotype 46 (43.4%); 2a genotype 7 (6.6%); 3a genotype 18 (17.0%); 3b genotype 3 (2.8%); 6a genotype 9 (8.5%); 1b/3b mixed type 13 (12.3%); and unidentified type 10 (9.4%). Prevalent genotypes of HCV were diverse, and 1b was the main genotype (43.4%), shown as in Table 2.

3.3 | The positive rates of HCV cAg detected by CMIA and ELISA

Among 106 HCV-infected patients, the positive rates of HCV cAg detected by CMIA and ELISA were 100% and 56%, respectively, which were statistically significant ($\chi^2 = 60.38$, $P = 0.000$). Among 1b genotype, the positive rates of HCV cAg were 100% (detected by CMIA) and 63% (detected by ELISA), with statistical significance ($\chi^2 = 20.85$, $P = 0.000$). Among 3a genotype, the positive rates of HCV cAg were 100% (by CMIA) and 61% (by ELISA), which was statistically significant ($\chi^2 = 8.69$, $P = 0.008$). Among 6a genotype, the positive rates of HCV cAg were 100% (by CMIA) and 44% (by ELISA), which was statistically significant ($\chi^2 = 6.92$, $P = 0.009$). Among 1b/3b mixed genotype, the positive rates of HCV cAg were 100% (by CMIA) and 61% (by ELISA), with statistical significance ($\chi^2 = 7.80$, $P = 0.015$). Among unidentified genotype, the positive rates of HCV cAg were 100% (by CMIA) and 30% (by ELISA), which were statistically significant ($\chi^2 = 10.77$, $P = 0.003$). There was no statistical significance in positive rates of HCV cAg detected by CMIA and ELISA among other subgenotypes ($P > 0.05$; See Table 3).

TABLE 1 General clinical characteristics of HCV-infected patients

Clinical characteristics	HCV-infected patients
N	106
Age	40 (18-78)
Sex	
Male	63 (59.4%)
Female	43 (40.6%)
HCV RNA, IU/mL	6.17 (5.51,6.67)
HCV Cag, fmol/L	947.44 (198.93,4355.07)
ALT, U/L	62 (43,122.25)
AST, U/L	50 (32,87.50)

3.4 | Comparison of expression levels of HCV RNA, HCV cAg, ALT, and AST in different genotypes

The levels of HCV RNA, HCV cAg, ALT, and AST in different genotypes were compared as following: the level of HCV cAg in 1b genotype was higher than that in 3b genotype and 1b/3b mixed genotype, with statistical significance ($U = 3.0$, $P = 0.006$, $U = 165$, $P = 0.014$). However, there was no statistical significance in the levels of HCV RNA, ALT, and AST ($P > 0.05$). Among other genotypes, expression levels of HCV RNA, HCV cAg, ALT, and AST were not statistically significant ($P > 0.05$; See Table 4).

3.5 | Correlation analysis between HCV RNA load and HCV cAg in different genotypes

The correlation between HCV RNA load and HCV cAg in different genotypes was analyzed: HCV RNA was positively correlated with HCV cAg in 1b genotype, with statistical significance (Spearman's correlation coefficient $r = 0.894$, $P = 0.04$). There was no correlation between HCV RNA and HCV cAg in other genotypes, without statistical significance ($P > 0.05$; See Table 5).

4 | DISCUSSION

Hepatitis C caused by HCV is a worldwide disease with a global infection prevalence about 3%.[10] Hepatitis C is known as "silent epidemic," because early clinical symptoms of most HCV-infected patients are untypical and easily ignored.[11] Without obvious symptoms, most HCV-infected patients have latent symptoms in acute stage and early phase of chronic infection, but with high-level

TABLE 2 HCV genotype distribution in Chongqing Municipality

Genotype	Case number	Frequency (%)
1b	46	43.4
2a	7	6.6
3a	18	17.0
3b	3	2.8
6a	9	8.5
Mixed type (1b/3b)	13	12.3
Unidentified type	10	9.4
Total	106	100

TABLE 3 Comparison of positive rates of HCV cAg detected by CMIA and ELISA

	CMIA			ELISA		
Genotype	Positive	Negative	Positive rates (%)	Positive	Negative	Positive rates (%)
1b	46	0	100*	29	17	63*
2a	7	0	100	4	3	57
3a	18	0	100**	11	7	61**
3b	3	0	100	1	2	33
6a	9	0	100***	4	5	44***
1b/3b	13	0	100****	7	6	54****
Unidentified	10	0	100	3	7	30
Total	106	0	100	59	47	56

*P = 0.000; **P = 0.008; ***P = 0.009; ****P = 0.015.

TABLE 4 Comparison of levels of HCV RNA, HCV cAg, ALT, and AST in different genotypes

Genotype	N	HCV RNA, IU/mL	HCV Cag, fmol/L	ALT, U/L	AST, U/L
1b	46	6.3 (5.7,6.6)	1710.4 (540.1,6325.3)	63.5 (46.0,120.7)	48.0 (32.0,82.3)
2a	7	6.3 (5.8,6.7)	2341.1 (445.4,2399.8)	54.0 (25.5,124.5)	62.0 (52.5,88.0)
3a	18	6.5 (6.1,6.8)	3226.9 (674.8,7734.4)	46.0 (42.3,101.5)	36.0 (29.5,82.7)
3b	3	6.2 (5.3,6.2)	60.3 (50.3,75.4)*	116.0 (79.5,124.0)	70.0 (51.0,71.5)
6a	9	6.2 (5.5,6.4)	786.3 (209.1,2822.9)	49.0 (31.0,67.0)	36.0 (29.0,50.0)
1b/3b	13	6.3 (5.8,7.2)	460.7 (270.0,733.2)**	101.0 (71.0,138.0)	98.0 (40.0,122.0)
Unidentified	10	5.5 (5.1,5.7)	26.3 (19.3,32.9)	54.5 (45.3,110.7)	50.0 (35.8,57.8)

*P = 0.006; **P = 0.014.

TABLE 5 Correlation between HCV RNA and HCV cAg in different genotypes

Genotype	Case number	Spearman's correlation coefficient r
1b	46	0.894*
2a	7	−0.360
3a	18	0.400
3b	3	0.500
6a	9	−0.122
1b/3b	13	−0.413
Unidentified	10	0.529

*P = 0.04.

viremia and elevated ALT levels. HCV RNA is usually detected earlier than anti-HCV after acute HCV infection.

HCV RNA becomes detectable within 2 weeks after exposure to HCV. HCV cAg can be detected in 1-2 days after appearance of HCV RNA, while anti-HCV cannot be detected until 8-12 weeks after infection.

HCV can be divided into six genotypes (from 1 to 6) according to the difference of nucleotide sequences, and each genotype has several subtypes which are represented by a, b, c. The geographic distribution of HCV genotypes is rather complex. The so-called epidemic subtypes—specifically 1a, 1b, 2a, and 3a— are widely distributed worldwide and account for a great proportion of the totality of HCV cases, especially in high income countries.[1,12] There are regional differences in distribution of genotypes, and genotype 1 is the most widely distributed around the world. In China, the most common HCV infection genotype is 1b, followed by 2a.[13] The genotypes in the north part of China are relatively single, with 1b and 2a as the main types. But there are various genotypes in the south part of China, with 1b as the major, 2a, 3a, 3b, and 6a occupy certain proportions, respectively. According to *the Guideline of Prevention and Treatment for Hepatitis in China* in 2004, *the Guideline of the American Association for the Study of Liver Diseases* in 2009 and 2011, and *the Guideline of the European Association for the Study of the Live* in 2011, HCV genotypes should be detected before treatment so as to make different treatment options. HCV genotype detection before treatment can predict the therapeutic effect of PEG-IFN-α in combination with ribavirin, which shows importantly clinical significance of HCV genotype detection. The research indicated that HCV infection genotypes in Chongqing became diversified, with 1b in primary position (38%). The proportion of 2a, 3a, 3b, and 6a is from 13% to 16%.[14] The study results were as follows: 1b genotype 46 (43.4%); 2a genotype 7 (6.6%); 3a genotype 18 (17.0%); 3b genotype 3 (2.8%); 6a genotype 9 (8.5%); 1b/3b mixed type 13 (12.3%); and unidentified type 10 (9.4%). 1b was the major sub genotype. All the results were consistent with literature contents.

Several published studies showing that patients infected with HCV genotype 1b may have a higher risk of developing HCC than those infected with other genotypes.[15-18] HCV core protein mutations (Gln70 and/or Met91) in HCV genotype 1b patients may be closely associated with HCC development and resistance to PEG-IFN/ribavirin (RBV) treatment.[3] The study detects a significantly higher rate of HCV RNA positivity in HCC patients than in control group. Furthermore, HCC patients harbors a higher rate of HCV 1b than general population, not influenced by the use of antiviral treatment as the multivariate analysis showed.[19]

In this study, the positive rates of HCV cAg were detected by CMIA (100%) and ELISA (56%), which shows the former higher than the latter ($\chi^2 = 60.38$, $P = 0.000$). The reason why the positive rate detected by CMIA was higher than that of ELISA was that ELISA could only detect free HCV cAg, while CMIA had a lower detection limit than ELISA and it could quantitatively test HCV cAg, including free HCV cAg and compounds of free HCV cAg and HCV-Ab, which greatly improved sensitivity of HCV cAg detection.[20] Quantitatively test HCV cAg with CMIA in HCV infection diagnosis had advantages, such as high positive rate, good specificity and sensitivity, short window period, and easy operation.

Detection of HCV RNA is a gold standard for diagnosis of HCV infection, but there are still various factors that affect detection results of real-time PCR, including easily-degradable RNA, poor stability, high demands for experiment, especially strict requirements on collection, preservation, and detection of samples and false-positive rate caused by cross-contamination. Detection of HCV cAg was first reported in 1996.[21] HCV virus particle is a capsule with a diameter of about 55.65 nm, HCV RNA and HCV core protein are encapsulated in it at a certain rate. HCV core protein is about 190aa. As an important indicator of HCV infection, its conservative amino acid sequence also plays an crucial role in virus proliferation and pathogenesis. The amount of HCV cAg in serum reflects the level of viremia to some extent. It has been reported abroad that without consideration of HCV genotypes, HCV RNA was correlated with HCV Ag.[22] Kesli et al[23] revealed that when compared to HCV RNA detection, HCV cAg's sensitivity, specialty, positive predictive value, and negative predictive value were 96.3%, 100%, 100%, and 89.7%, respectively. Moghaddam SM pointed out that there was correlation between HCV Ag level and HCV RNA level in liver and serum.[24] Johannes Vermehren et al[25] suggested that although HCV cAg detection could not replace HCV RNA detection, it could assist in predicting disease progress and detecting antiviral effect. The study found that HCV RNA was positively correlated with HCV cAg in genotype 1b when genotype was considered, with statistical significance $P < 0.05$ (Spearman's correlation coefficient $r = 0.894$, $P = 0.04$). There was no correlation between HCV RNA and HCV cAg in other genotypes, without statistical significance ($P > 0.05$). The expression levels of HCV cAg in 1b genotype were higher than that in 3b genotype and 1b/3b mixed genotype, with statistical significance ($P < 0.05$; $U = 3.0$, $P = 0.006$, $U = 165$, $P = 0.014$). Expression levels of HCV RNA, ALT, and AST did not have statistical significance ($P > 0.05$). Correlation was found between HCV cAg and HCV RNA in 1b genotype.

In conclusion, HCV core antigen detection and quantification thus represent a valuable alternative to HCV RNA testing for diagnosing HCV infection in genotype 1b. This is particularly interesting for low resource countries, because HCV RNA measurements need well equipped and specialized laboratories, and are quite expensive. HCV cAg could be an early detection indicator to support HCV infection diagnosis, and it also reflected level of virus replication. Despite our data suggest the association exist between HCV cAg and HCV RNA in genotype 1b,a prospective study with larger number of samples will be needed to confirm our results, especially considering the strict correlation existing between Genotype 1b and HCV Ag.

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