Original Article

Logistic Regression Analysis of Influencing Factors on Serum ALT and HCV RNA Changes in Patients with Chronic Hepatitis C

Cheng-bao Wang^{1,2}, Jian-jie Chen¹, Hong-ming Nie¹, Feng Gao², Hua Lv¹ and Hong-ding Li¹

Objective This study was undertaken to investigate the influencing factors on serum ALT level and hepatitis C virus (HCV) RNA titer in chronic hepatitis C (CHC) patients.

Methods All patients enrolled into this study were anti-HCV positive. Retrospective tracing method was applied to detect serum ALT level and HCV RNA titer and to collect general information of the patients such as genders, age groups, interferon medication history, infection pathways, height and weight. Then the multi-factor analysis was adopted with the application of binominal logistic regression mode.

Results The abnormal rate of ALT level was positively correlated to HCV RNA and gender while negatively correlated to interferon medication history and age group, with Wald value of the 4 factors as 39.604, 11.823, 18.991 and 7.389, respectively. The positive rate of HCV RNA was negatively correlated to interferon medication history and gender while positively correlated to ALT level, with corresponding Wald value of the 3 factors as 81.394, 7.618 and 27.562, respectively.

Conclusions The normal ALT level in HCV infected patients was associated with viral load, age, gender and interferon medication history, while the normal rate of HCV RNA titer was closely associated with gender, interferon medication history and ALT level.

Key words: Multi-factor logistic regression analysis; Hepatitis C virus; Chronic Hepatitis C; Serum ALT level; HCV RNA

As an important cause of human chronic hepatitis, hepatitis C virus (HCV) frequently correlated to cirrhosis and increased risk of hepatocellular carcinoma.¹⁻³ Approximately 2.2% of the global population is infected with HCV, and 70%–80% of exposed individuals suffer from a chronic infection.^{4,5} In China, a seroprevalence rate of anti-HCV was 0.58% that has been reported in a recent study,⁶ which is lower than the global rate; however, HCV infection is still a major public health problem because of the large population base in China.¹

For the patients of hepatitis C, serum alanine aminotransferase levels and serum HCV RNA titer are two important evaluation indexes. Although some reports showed that there may be clinical relevance between them,^{7,8} there still has some other factors which may also affect the levels of alanine aminotransferase and serum HCV RNA. It has been reported that clearance rate (anti-HCV positive, HCV RNA negative) of HCV RNA was gender-related with higher negative transforming rate in females,⁹ while other report

showed there was no statistical difference in HCV RNA clearance rate between different genders.¹⁰ Some papers also reported that higher ALT levels in patients with hepatitis C have higher viral load.¹¹ Another group suggested that no significant difference in viral load existed between patients with abnormal ALT levels and those with normal ALT levels.¹² Serum HCV RNA titer had no correlation with the ALT level, which could not reflect the degree of liver histological damage.^{13,14} We aimed to make clear the correlation of serum ALT level and HCV RNA titer and their influencing factors in patients with chronic hepatitis C in mainland of China. This study was carried out through multi-centered and large-sampled investigation, with 1077 cases of chronic hepatitis C collected from 12 cities in China from March to December in 2009, and was analyzed by multi-factor logistic regression in terms of gender, age group, interferon medication history, infection pathway and BMI value.

MATERIALS AND METHODS

Clinical data

All the 1077 cases were inpatients or outpatients

¹Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China; ²Linyi People's Hospital, Linyi City, Shandong 276003, China
Correspondence: Jian-jie Chen, E-mail: Jianjie_chen@hotmail.com

admitted by 18 hospitals from 12 cities of China (Shanghai, Beijing, Nanjing, Shenzhen, Zhengzhou, Jinan, Changzhou, Nantong, Nanning, Chengdu and Guangzhou). Among them, 551 cases (51.2%) were male, with mean age as 47.3 ± 14.05 years old, 42 cases (3.9%) were less than 20 years old, 532 cases (49.4%) were 20-50 years old and 503 cases (46.7%) were elder than 50 years old. And 765 cases did not own interferon medication history, 673 cases (62.5%) were infected through blood transfusion. All patients having shown anti-HCV positive.

Quantitative approaches to serum ALT level and HCV RNA titer

Chemical reagent strip method and dual-probe real-time fluorescence quantitative method were applied to detect ALT levels and HCV RNA titer, respectively. The assays were unified detection by central laboratory (Adicon Clinical Laboratories, USA).

Index quantification

All possible indexes influencing ALT level and HCV RNA titer were quantified based on actual values or classifications (Table 1).

Statistics

All data were processed with statistical package of SPSS 17.0 for Windows. With binomial logistic regression model and Forward: Wald method applied, variables were selected into the equation at significance level of 0.05 or eliminated at 0.1.

(Table 2). According to regression coefficient, higher HCV RNA titer was related to increasing possibility of abnormal ALT level in male patients, while the possibility in patients with interferon medication was descending. Wald values showed that HCV RNA contributed most to abnormal ALT level prior to interferon medication history, gender and age group in descending order. And the corresponding abnormal rates of the three age groups (< 25 years old, 25-50 years old and >50 years old) were 46.8%, 59.5% and 53.2% with statistical difference in comparison among 3 groups ($\chi^2 = 6.913$, $P = 0.032$).

The influencing factors on serum HCV RNA titer

HCV RNA were negative in 154 cases and positive (abnormal) in 923 cases, which were influenced by independent variables such as gender, age, group, ALT level, interferon medication history, infection pathway and BMI in addition to dependent variable of HCV RNA titer in binomial logistic regression analysis. Statistical results suggested that significant difference only existed in variables such as gender, interferon medication history and ALT level ($P < 0.05$) (Table 3). Based on regression coefficient, decreasing possibility of positive HCV RNA was related to male patients with interferon medication history, while the chance of getting HCV RNA positive in patients with high ALT level increasing. Interferon medication history was the leading factor contributed to positive HCV RNA prior to ALT level and gender in descending order according to Wald values.

RESULTS

The influencing factors on serum ALT level

ALT level were normal in 477 cases and abnormal (positive) in 600 cases, which were influenced by independent variables such as gender, age, group, HCV RNA titer, interferon medication history, infection pathway and BMI in addition to dependent variable of ALT level in binomial logistic regression analysis. The results suggested that all variables had significance except for infection pathway and BMI ($P > 0.05$)

DISCUSSION

ALT level and HCV RNA titer are two important indexes in evaluating hepatitis C, and reports have claimed that liver fibrosis progression is associated with elevated ALT.¹⁵ As HCV RNA titer can directly reflect replication of virus, most studies have revealed some influencing factors on serum ALT level and HCV RNA changes in patients with chronic hepatitis C.

In this study, the factors affecting serum ALT level and HCV RNA titer including gender, age, HCV

Table 1. Quantified form of indexes

Variables	Meaning	Standard for quantification
$Y_1 (X_4)$	ALT	As Y_1 , 1 for abnormal and 0 for normal; as X_4 , measured value was adopted
$Y_2 (X_5)$	HCV RNA	As Y_2 , 1 for abnormal and 0 for normal; as X_5 , logarithm of measured value was adopted
X_0	Gender	1 for male and 0 for female
X_1	Age group	0 for those ≤ 25 years, 1 for 25-50 years and 2 for ≥ 50 years
X_2	Interferon medication history	1 for those having interferon medication history and 0 for no
X_3	Infection pathway	1 for infection through blood transfusion and 0 for other infection pathways
X_4	BMI value	1 for BMI value ≤ 18.5 , 2 for 18.5-24 and 3 for 24

Table 2. Influencing factors on abnormal ALT level through binomial logistic regression analysis

Factors	B	S. E.	Wald	P	Exp (B)	95% CI for EXP (B)	
						Lower	Upper
HCV RNA (log ₁₀)	0.185	0.029	39.604	0.000	1.204	1.136	1.275
Gender	0.451	0.131	11.823	0.001	1.570	1.214	2.030
Age group			7.389	0.025			
Age group (1)	-0.475	0.260	3.345	0.067	0.622	0.374	1.035
Age group (2)	0.194	0.135	2.073	0.150	1.214	0.932	1.581
Interferon medication history	-0.638	0.146	18.991	0.000	0.528	0.397	0.704

Notes: B was for regression coefficient, S.E. for standard error, Wald for Wald value, P for significance level and Exp (B) for odds ratio estimate.

Table 3. Influencing factors on abnormal HCV RNA titer through binomial logistic regression analysis

Factors	B	S. E.	Wald	P	Exp (B)	95% CI for EXP (B)	
						Lower	Upper
Gender	-0.531	0.192	7.618	0.006	0.588	0.403	0.857
Interferon medication history	-1.734	0.192	81.394	0.000	0.177	0.121	0.257
ALT	0.015	0.003	27.562	0.000	1.015	1.010	1.021

Notes: B was for regression coefficient, S.E. for standard error, Wald for Wald value, P for significance level and Exp (B) for odds ratio estimate.

infection pathway and BMI were analyzed by multi-factor logistic regression. The results suggested that ALT level was most likely to be abnormal in male patients with elevated HCV RNA titer, aging between 25-50 years old and with no interferon medication history. While multi-factor analysis showed that the OR values of infection pathway and BMI were 1.145 ($P = 0.319$) and 1.158 ($P = 0.197$), respectively, which suggested that infection pathway and BMI were not significantly correlated with positive rate of serum ALT. Though BMI was reported to have close correlation with liver fibrosis progression,¹⁵ we still hold that this correlation may be uncertain. In this study, there were 340 cases (31.5%) with undetermined infection pathways, and the exact time when the patients were infected could not be confirmed. Thus the relationship between the time of infection and serum ALT level and HCV RNA titer could not be confirmed either.

The positive rate of serum HCV RNA was associated with gender, interferon medication history and serum ALT level. And female patients with elevated ALT level and no interferon medication history had shown higher abnormality of HCV RNA. Multi-factor analysis showed that the OR values of infection pathway, age and BMI were 0.894 ($P = 0.588$), 1.123 ($P = 0.459$) and 0.948 ($P = 0.751$), respectively, which suggested that infection pathway, age and BMI were not significantly correlated with positive rate of serum HCV RNA. So we need to pay special attention to the detection of ALT level and HCV RNA titer in female patients with high ALT level and no interferon medical history in clinical practice.

By comprehensive comparison, our study have found out the significant influence of interferon medication history on ALT level and its leading role on HCV

RNA titer. Thus, we have confirmed the beneficial effects of applying interferon on sustaining normal liver function and promoting negative transforming of HCV RNA. Particularly, we have found more female patients (48.9%) expressed normal ALT level than males (39.9%), with mean ALT level as 65.50 ± 59.38 U/L and 78.45 ± 74.60 U/L ($P < 0.05$), respectively. However, the negative transforming rate of HCV RNA was significantly lower in female patients (12.2%) than in males (16.3%), with the mean logarithm HCV RNA titer 5.18 ± 2.23 copies/ml and 4.97 ± 2.45 copies/ml, respectively. This may relate to higher estrogen level in females and the gene polymorphism between genders. It was reported that estrogen was a powerful endogenous antioxidant in decreasing ester peroxide level in liver and blood and thus lowering incidences of hepatic fibrosis.¹⁶ And other papers also show that women carrying the genotype GG (position, -1082 bp) can produce more IL-10. Higher levels of IL-10 present in those individuals are associated with a higher risk of an inefficient clearance of HCV and the development of a chronic HCV infection together with a lower risk of progression to cirrhosis in female patients.¹⁷

In conclusion, it has proved that normal ALT level in HCV infected patients was associated with viral load, age, gender and interferon medication history, while the normal rate of HCV RNA titer was closely associated with gender, interferon medication history and ALT level. All these have supported the application of interferon, facilitated disease prediction and further proved the close correlation between serum ALT level and HCV RNA titer in patients with chronic hepatitis C.

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