Original Article

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Hepatitis C virus infection in the general population: A large community-based study in Mianyang, West China

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Summary **Hepatitis C virus (HCV) infection remains a major public health problem. The objective of the current study was to reveal the seroepidemiology of HCV in the general population in Mianyang City. This study collected 438,575 blood samples from participants who had enrolled in the National Science and Technology Development Project and their demographic information, and then evaluated HCV antibody and alanine aminotransferase (ALT) levels. The overall anti-HCV positive rate was 0.80% (3,491/438,575) in the Mianyang general population, and it was 1.19% in rural population and 0.20% in urban. Anti-HCV positive rate increased with age, peaked at 45-54 years (2.01%), and then decreased. Anti-HCV prevalence was higher in males (0.89%) than that in females (0.73%). The prevalence of anti-HCV in participants with a history of blood transfusion, surgery, or with a previous diagnosis of hypertension was higher. The abnormal ALT levels (> 40 IU/L) were observed in 50.11% and 7.74% of anti-HCV positive and negative groups, respectively. In anti-HCV positive groups, the rate of abnormal ALT levels was higher in 55-64 age groups, male, and rural population. Though Mianyang was a low endemic area for HCV infection, the alarming fact was the large number of abnormal ALT levels in patients related to hepatitis C. This revealed delayed diagnosis and treatment of HCV infections. It is a necessity to promote early diagnosis and timely treatment of HCV infections.**

Keywords: Seroepidemiology, hepatitis C virus antibody, alanine aminotransferase, general population, China

1. Introduction

Hepatitis C is an infectious liver disease, caused by the hepatitis C virus (HCV) (*1*). The infection is often asymptomatic especially in its early stages, but once established, 74% to 86% of newly infected persons will develop chronic infection and the chronic stage constitutes one of the leading causes of cirrhosis and hepatocellular carcinoma (HCC) (*2,3*). HCV infection is a major public health problem in both developing and developed countries. The World Health Organization estimated that about 130 to 170 million people, 2% to 3% of the world's population, currently are HCV infected. Moreover, there are about 3 to 4 million new cases every year (*4*).

In 2012, HCV infection was the fourth most commonly reported infectious disease in China following hepatitis B virus infection, pulmonary tuberculosis and dysentery (*5*). Recent data estimated that up to 25 million Chinese were HCV infected (*6*). The prevalence of HCV infection ranged from 0.43% to 3.2%, and varied geographically and temporally in China (*7-9*). During the past decades, most of studies related to HCV infection in China focused on hospital based and high risk population groups including blood donors and receivers, drug abusers, individuals with HIV, and sex workers (*10-13*); while there were only a few large-scale studies in China which concentrated on HCV prevalence in the general population (*8,9,14*).

On the basis of the availability of new, direct-acting antiviral medications, we have entered a new era of hepatitis C therapeutics with an enormous opportunity to prevent morbidity and mortality among

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people with HCV infection (*15*). In this regard, a good understanding of HCV prevalence is important for prevention and treatment of HCV. Here, using blood samples and data that had been collected from the National Science and Technology Development Project for infectious disease prevention and control in Mianyang, Sichuan province, we conducted a seroepidemiology study to explore the HCV prevalence and the alanine aminotransferase (ALT) level to investigate the clinical and virological characteristics as well as treatment outcomes in the general population in Mianyang. We believe this study will help to devise strategies by health policy makers for control of hepatitis C disease.

2. Materials and Methods

2.1. *Survey design*

The National Science and Technology Development Project which was carried out from February 2010 to June 2012 had been initiated to collect data on hepatitis B virus (HBV), HCV and tuberculosis infection status in the general population in Mianyang, the second largest city of Sichuan province (Figure 1). The project used a cluster sampling design. There are nine administrative divisions: two districts and seven countries. One district of Fucheng and one country of Anxian, were selected randomly (Figure 1). Then, 8 sub-districts and 14 towns from Fucheng, and 18 towns from Anxian were randomly selected. Finally, within each town/sub-district, two villages/communities were selected according to economic level. In these participant sites that we selected, the study included all local residents and migrant workers who had lived there for 6 months.

After the staff received appropriate training from the lead researchers for this project, data collection was conducted in examination centers at local health stations and community clinics that were located in sub-district/towns that the project had chosen. According to a standard protocol, trained staff conducted face-to-face interviews *via* questionnaires after obtaining written consent from the participants. The questionnaire collected demographic information (including gender, age, and area of residence) and medical history information (including history of diabetes, history of hypertension, family history of hepatocellular carcinoma, blood transfusion and surgical intervention); and each copy of the questionnaire had a unique identification number. After the interview, a 5-mL serum sample, labeled with the same identification number as questionnaire, was collected from each participant. Blood samples were properly stored in a low temperature container (controlled from 4-8°C), and were transported daily to laboratory test hospitals for sample processing and serological testing.

For HCV and ALT testing, available blood samples after HBV testing were used. The study was approved by the Ethics Committee of West China Hospital, Sichuan University.

Figure 1. Map of Mianyang, China, showing the location of Mianyang (the star) and the two counties (black areas) selected for sampling in the study.

2.2. *Laboratory testing*

Commercial third-generation enzyme immunoassay kits (ELISAs) (Xinchuang Core Anti-HCV ELISA kit, Xiamen, China) were used for HCV antibody testing. Verification of positive samples was carried out by retesting the samples using the same kits. Only samples that were positive on both tests were considered to be true positive, which was the indicator of previous HCV contact history.

Serum ALT quantitation was performed after being screened for anti-HCV antibodies. Quantitation was achieved using a coupled enzyme and indicator reaction that utilizes pyruvate for a kinetic determination of NADH consumption measured by an automated biochemical analyzer (CS-T300, Dirui, China). Abnormal ALT levels were defined as greater than 40 IU/L.

2.3. *Statistical analysis*

We used Chi-square test to compare anti-HCV positive rates by different characteristics. We also used Chi-square test to compare the ALT level by age, sex and area. SPSS 17.0 software located in the Epidemiology and Biostatistics Department of West China School of Public Health at Sichuan University was used for analysis. p value < 0.05 was considered to be statistically significant.

3. Results

3.1. *Demographic characteristics*

A total of 438,575 serum samples were available for HCV screening from the participants. Of these participants, 175,161 (39.94%) were from the urban area and 263,414 (60.06%) from rural area. There were 200,942 (45.8%) male and 237,633 (54.2%) female participants. The age of the participants ranged from 1 to 90 years, with a mean of 35.91 ± 21.15 years old.

Table 1. Prevalence of anti-HCV stratified by different characteristics in Mianyang

Characteristics	Total samples	Anti-HCV positive case	Anti-HCV positive rate (%)	χ^2	*p* value
Age groups					
1-14	94349	71	0.08	2623.10	< 0.001
15-24	75145	138	0.18		
25-34	29949	154	0.51		
35-44	72393	941	1.30		
45-54	60676	1243	2.01		
55-64	62015	767	1.24		
≥ 65	42628	177	0.41		
Sex					
Female	237633	1725	0.73	32.26	< 0.001
Male	200942	1766	0.89		
Area					
Urban	175161	345	0.20	1325.25	< 0.001
Rural	263414	3146	1.19		
HBsAg positivity					
No	407239	3331	0.82	34.81	< 0.001
Yes	31336	160	0.51		
Blood transfusion					
No	435999	3434	0.79	65.87	< 0.001
Yes	2576	57	2.21		
Surgery					
No	409317	3085	0.75	138.98	< 0.001
Yes	29258	406	1.39		
History of hypertension					
No	420783	3318	0.79		
Yes	17792	173	0.97	7.30	0.007
History of diabetes					
No	436683	3474	0.80	0.25	0.62
Yes	1892	17	0.90		
Family history of HCC					
No	437857	3489	0.80	2.44	0.12
Yes	718	2	0.28		

Moreover, all the individual samples were categorized into seven age groups: 1-14, 15-24, 25-34, 35-44, 45-54, 55-64, ≥ 65. The proportions of these age groups were 21.5%, 17.1%, 6.8%, 16.5%, 14.1%, 14.1%, 9.8%, respectively.

3.2. *Anti-HCV positive rate*

3,491 were anti-HCV positive by ELISA, and the overall anti-HCV prevalence was 0.80% (3491/438,575). Statistical differences were observed considering the age group criterion. Anti-HCV prevalence was lowest in the 1-14 years old group (0.08%, 71/94,349). Anti-HCV prevalence increased with age, peaked at the 45-54 years old group (2.01%, 1,243/60,676), and then decreased. The individuals in age group 45-54 years showed an about 25-fold higher rate of anti-HCV seropositivity when compared with the individuals in age group 1-14 years. Overall, the individuals aged between 35-64 years represented 85% (2,951/3,491) of the anti-HCV seropositive subjects (Table 1, Figure 2).

The prevalence of anti-HCV was 0.89% in males (1,766/200,942) and 0.73% in females (1,725/235,908). The sex-specific prevalence of anti-HCV showed higher rates in male patients in each age group, except for individuals aged 25 to 34 years. Both males and females showed the highest anti-HCV prevalence in the age group 45-54 years. The difference in sex-specific prevalence widened with age and reached a maximum in the 45-54 year-old age group, followed by a decrease with advancing age (Table 1, Figure 3).

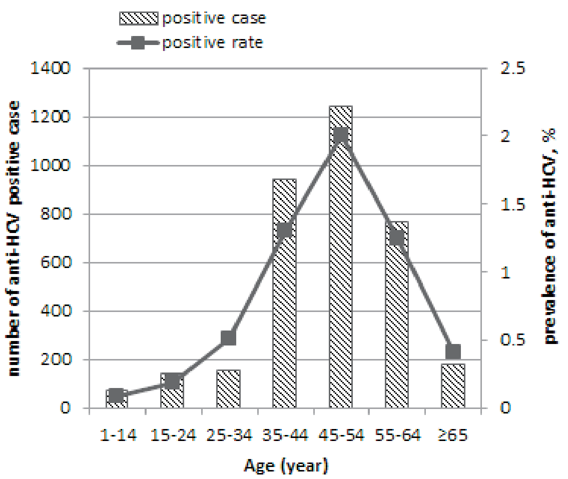

Figure 2. Overall characterization of anti-HCV by age group. Bars represent the number of anti-HCV positive cases in each group indicated by left vertical axis, and the squares represent the prevalence in each group indicated by right vertical axis. The horizontal axis represents the age ranges.

The overall prevalence of anti-HCV in rural areas was

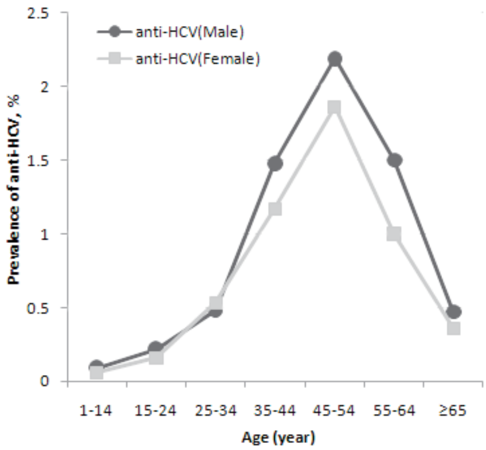

Figure 3. Sexual characterization of anti-HCV by age group. The left vertical axis represents the prevalence of anti-HCV. The dots represent the prevalence in males in each group, and the squares represent the prevalence in females in each group. The horizontal axis represents the age ranges.

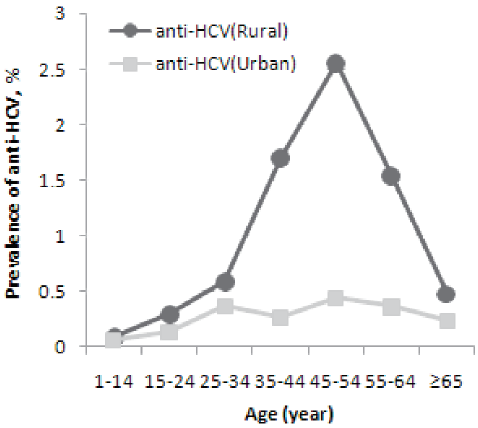

Figure 4. Regional characterization of anti-HCV by age group. The left vertical axis represents the prevalence of anti-HCV. The dots represent the prevalence in rural areas in each group, and the squares represent the prevalence in urban areas in each group. The horizontal axis represents the age ranges.

1.19% (3,146/263,414), which was much higher than that in urban areas, 0.20% (345/175,161). The individuals living in rural areas represented 90% of the anti-HCV seropositive subjects. The disparity in prevalence between rural areas and urban areas increased with age such that the largest differences were apparent in individuals of 45-54 years of age. In individuals aged 45-54 years, the prevalence of HCV infection was 4.8 times higher among rural areas than urban areas (Table 1, Figure 4).

There were 31,336 people out of the population of 438,575 in Mianyang whose serum tested positive for HBsAg, and the HBV infection rate was 7.15%. There were 160 people who were anti-HCV positive among the 31,336 HBsAg-positive patients. The HCV concurrent infection rate was 0.51%, slightly lower than the HCV infection rate (0.80%) of the local general population. Significant differences were observed for blood transfusion, surgery and history of hypertension regarding the prevalence of anti-HCV. The prevalence of anti-HCV in participants with a history of blood transfusion, surgery, or with a previous diagnosis of hypertension was higher (Table 1). However, a previous diagnosis of hypertension might not be truly related to HCV prevalence. Because the sample size of the study was large, any small difference could be detected.

3.3. *ALT levels*

There were 13 missing ALT values in the anti-HCV positive group. The overall prevalence of abnormal ALT level was 8.07%. It was higher in the anti-HCV positive group (50.12%) than in the anti-HCV negative group (7.74%).

In the anti-HCV positive group, the prevalence of abnormal ALT levels increased with age, from 14.08% in the 1-14 year group to 57.92% in the 55-64 year group, and then decreased. The prevalence of abnormal ALT was higher in males (57.25%) than in females (42.82%), and it was also higher in rural areas (52.50%) than in urban areas (28.28%). See Table 2.

Table 2. Serological features of abnormal ALT prevalence in anti-HCV positive group

Items	NO. anti-HCV positive	NO. ALT > 40 IU/L	Abnormal ALT rate (%)	χ^2	*p* value
Total	3478	1743	50.12		
Age groups				190.34	< 0.001
1-14	71	10	14.08		
15-24	137	29	21.17		
25-34	153	31	20.26		
35-44	939	482	51.33		
45-54	1238	689	55.65		
55-64	763	442	57.92		
≥ 65	177	60	33.90		
Sex				72.44	< 0.001
Female	1719	736	42.82		
Male	1759	1007	57.25		
Area				72.57	< 0.001
Urban	343	97	28.28		
Rural	3135	1646	52.50		

4. Discussion

As the fourth most commonly reported infectious disease in China, HCV infection can be expected to make up an increasingly large portion of the disease burden in the future. A seroepidemiology survey of hepatitis C infection is important for prevention and treatment of the disease (*16*). In 1992, the first nationwide cross-sectional seroepidemiologic survey of hepatitis C infection with a total of approximately 68,000 participants showed the prevalence of anti-HCV was 3.2% in the general population aged from 1 to 59 years (*8*). However, two recent studies reported a lower prevalence in the general population. In 2006, China Center for Disease Control and Prevention (CCDC) reported that the overall prevalence of anti-HCV was 0.43% among the population of 1 to 59 years old on the basis of 78,746 blood samples (*10*); in 2007, another study with 9538 serum samples collected from 6 regions reported that the overall positive rate of anti-HCV was 0.58% (*9*). New regulations on forbidding paid blood donations and the reuse of unsterilized needles for medical injections, increased health education, and more accurate diagnostic technologies in recent years might explain differences among these findings.

Our study reported that the positive rate of anti-HCV in the general population of Mianyang was 0.80% (3,491/438,575), which is higher than the previously reported rates in 2006 and 2007. The rate was very close to the result of a screening of 157,168 people in Jiangsu province where the total positive rate of anti-HCV was 0.79% (*15*).

Each age group contained at least one HCV infected person in Mianyang, but the anti-HCV positive rates differed. In spite of different gender and residential areas, the anti-HCV positive rate increased with age, reached a peak at 54 years old, and then declined. This implied a steady cumulative increase in incidence, probably caused by the sporadic transmission of virus persisting in the community/village through the years, and the high rate of chronic infection related to the natural history of HCV infection. After 54 years old, an increase in mortality among HCV-infected people may explain the decrease in prevalence of HCV infection.

Our analysis also found that individuals aged from 35 to 64 years represented 85% of the anti-HCV seropositive subjects. This finding was similar to a report from the United States that individuals born between 1945 and 1965 (aged from 40 to 59) comprised 81% of all chronic HCV infections (*17*). Given that, the Centers for Disease Control and Prevention of the U.S recommended a 1-time HCV test for all people born during that period (*18*). This recommendation could help to identify most individuals living with HCV. With implementation of this strategy, the U.S potentially averted approximately 120,000 deaths caused by HCV infection (*19*).

Interestingly, HCV infection disproportionately affected men more than women in this survey. Males showed a 1.2 times higher HCV infection rate than females, whereas other studies have reported equality between sexes or even female predominance in HCV infection (*8,20-22*). The underlying reason of male predominance in this study is still not clear. However, studies have demonstrated that, on average, about 20% of HCV infected individuals would spontaneously clear the virus after initial infection, and women were more likely to clear the virus spontaneously (*23,24*). In addition, we hypothesized that there may be more chances for men to be infected by HCV through unhealthy lifestyles or behaviors, such as smoking, drinking, poor hygiene, and unhealthy sexual activities.

We also found significant regional differences in the anti-HCV positive rate in Mianyang. Most of the HCV-infected persons resided in rural areas, which was inconsistent with previous studies in China (*16,25*). We suppose that this phenomenon was related to commercial blood selling in rural areas. Some studies have demonstrated that paid blood donors living in villages have comparatively higher anti-HCV rates (*26,27*). Before 1998, there were a number of commercial blood donors living in rural areas of China. These blood donors sold blood to unlicensed private blood collection centers for payment (*28*). Some of these illegal centers used unsafe blood collection methods, such as the reuse of none-sterilized needles and reinfusion of pooled red blood cells from multiple donors, which could easily lead to HCV infection. Given the greater burden of infection in rural areas, appropriate prevention measures to control the transmission of virus in rural areas were urgent. Health education, more thorough screening for HCV infection and early link of age-to-care and treatment initiation in rural areas were critical.

Although hepatitis B and hepatitis C have similar transmission routes, and although there was no vaccine for prevention of HCV, the study found that the HCV and HBV infection rates were significantly different in the general population in Mianyang (0.80% *vs*. 7.15%). Among the HBsAg-positive patients, the HCV concurrent infection rate was 0.51%, which is lower than that reported in other literature (*29,30*). Though there was a small amount of HBV and HCV coinfection, patients with dual HBV/HCV infection have a higher risk of progression to cirrhosis and decompensated liver disease than those in patients with monoinfection (*31,32*). So it is important for early detection and treatment of coinfection.

Participants with a history of blood transfusion had a higher prevalence of HCV infection in this study. In China, several studies have found that a history of blood transfusion was the most prevalent risk factor for HCV infection (*14,21,25,33*). This may be associated with commercial plasma donation in rural areas of China in the 1980s. Our study also found that participants with a history of surgery had a higher prevalence of HCV. In the past, in some township hospitals, there were poor sterilization procedures and no HCV detection before surgery, which could easily lead to HCV infection.

ALT levels were related to HCV infection status in Mianyang. The anti-HCV positive group had a higher prevalence of abnormal ALT compared with the anti-HCV negative group. The association between abnormal ALT and gender was consistent with previous studies, which reported that males were associated with a higher prevalence of abnormal ALT than females (*34,35*). However, unlike previous studies, we found that individuals ≥ 65 years did not have a higher prevalence of abnormal ALT in our study (*36*). Because ALT was presumed to be a marker of hepatic inflammation, our finding demonstrated that HCV infection could lead to chronic necro-inflammatory hepatic damage. Moreover, some prospective studies showed that persistently abnormal serum ALT levels were strongly associated with high incidences of HCC in individuals positive for anti-HCV (*37,38*). However, there usually were no symptoms in HCV-infected individuals when ALT was slightly elevated. Once symptoms appear, most HCV infected persons have already developed HCC (*38*). Since abnormal ALT comprised a large proportion of individuals infected with HCV in the current study, it is important for these people to receive early antiviral treatment and regular follow-up to reduce the risk of developing HCC.

There are several limitations that should be considered in this study. First, HCV virological assessments including HCV RNA levels and HCV genotypes were not performed. Our conclusions drawn from HCV seroprevalence estimates was weakened by the limitation of antibody testing for distinguishing between past and current infection. Library testing was conducted in local township hospitals or community hospitals. However, HCV RNA and HCV genotypes tests require a full set of equipment and complicated techniques, which could not be achieved in these hospitals. Further studies need to be done to calculate the current HCV infection rate and HCV genotype distribution in Mianyang. Second, as this was a cross-sectional survey, we could only find that anti-HCV prevalence was associated with the age at the time of survey, but can't determine whether it is related to the year of birth or not. To better explore birth cohort effects, further research requires direct measurements or estimation of more representative birth-specific prevalence rates. Third, we did not collect enough information on the potential exposure to HCV infection, such as blood donation, family history of HCV infection, and dental therapy, so we could not determine how HCV spread in Mianyang. Despite these disadvantages, to the best of our knowledge, this is the largest seroepidemiological study concerning the prevalence of anti-HCV in the general population.

In conclusion, this large-scale cross-sectional study shows that anti-HCV prevalence among the general population in Mianyang is slightly higher than the national average prevalence. Insights from the analysis of this large-scale HCV seroepidemiological survey are fundamental to guide future HCV research and other interventions. Information from this study will also be useful for government to make policy for HCV treatment and prevention scientifically.

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