ABSTRACT

Objectives: Little is known about hepatitis B virus (HBV) infection in patients with hepatitis C virus (HCV) infection in China. This study aimed to evaluate the prevalence, clinical characteristics, viral interactions and host genotypes of HBV/HCV dual infection compared with HCV monoinfection.

Study design: A cross-sectional study.

Setting: China.

Participants and methods: 997 patients with HCV from 28 university-affiliated hospitals in China were enrolled in this research. Patients were divided into two subgroups.

Results: The prevalence of HBV infection in patients with HCV was 4.11% (41/997). The age-specific prevalence of HBsAg was 0.70%, 3.97% and 5.85% in groups aged 18–30, 30–50 and >50 years old (p=0.057), respectively. Patients with HBV/HCV dual infection and patients with HCV monoinfection had similar HCV viral loads (5.80±0.89 vs 5.83±1.00 log10 IU/mL, p=0.904). The dominant HCV genotype was 1b in both groups (53.65% vs 56.90%, p=0.493). The protective C allele in IL-28B (rs12979860) was also the dominant allele type in both patient groups (85.36% vs 83.99%, p=0.814). Patients with HBV/HCV dual infection had a higher ratio of liver cirrhosis and hepatic decompensation than patients with HCV monoinfection (39.02% vs 17.69%, p=0.001; 31.70% vs 12.13%, p=0.001).

Conclusions: The HBV burden was moderate in HCV-infected patients in China. Liver cirrhosis was more common in patients with HBV/HCV dual infection, suggesting the need for closer monitoring of dual-infected individuals.

Trial registration number: NCT01293279; Post-results.

INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the most common causes of chronic liver disease, cirrhosis and hepatocellular carcinoma, affecting approximately 350 million and 170 million people worldwide, respectively.1-5 In China, HBV and HCV affect about 93 million and 10–30 million people, respectively. Dual infection with HBV and HCV is not uncommon because the two viruses share similar paths of transmission, especially in areas where they are endemic.2

The worldwide prevalence of HBV/HCV dual infection varies in different regions because of the different geographical distribution of the two viruses. Studies from the USA, Taiwan, Japan, India, Italy and China
have found an estimated prevalence of HBV/HCV dual infection of approximately 3.4–23% in hepatitis B surface antigen (HBsAg)-positive patients.\textsuperscript{6–8} The prevalence of HBV infection among patients with HCV in the USA was estimated to be 1.3–5.8%.\textsuperscript{6–8} However, most information on HBV/HCV dual infection has come from studies on populations with chronic HBV infection, especially in China. Very little is known about the prevalence of HBV/HCV dual infection among patients with HCV in China because of the lack of multicentre large-scale studies.\textsuperscript{9}

HBV/HCV dual infection is of great interest, with studies showing interactions between these two viruses. A critical question that has not been answered is whether HBV and HCV interfere with each other’s life cycles during HBV/HCV dual infection. Some studies have shown that HBV may inhibit HCV RNA replication,\textsuperscript{10} while others have proved the total opposite, with HCV RNA levels being the same in both patients with HBV/HCV dual infection and those with only HCV infection.\textsuperscript{7} With such controversial discoveries, it appeared important to better understand viral interactions in HBV/HCV dual infection.

The clinical characteristics of patients with HBV/HCV dual infection are important in designing treatment strategies. Moreover, many aspects of dual infection remain largely unknown, including biochemical and virological characteristics and host genotypes.\textsuperscript{11} These variables may be associated with disease severity and are thus important in therapeutic management.

There are even fewer data available for patients with HBV/HCV dual infection in China. In this study, we evaluated dual HBV/HCV infection in Chinese patients with HCV by analysing epidemiological, biochemical and virological characteristics, host genotypes and the prevalence of cirrhosis.

METHODS

Materials and study design

From February to June 2011, 1012 HCV-positive patients were enrolled from the outpatient facilities of 28 university-affiliated hospitals across China. All patients in this study had to meet the following two criteria: 18 years or older and HCV infection confirmed or reconfirmed (antibody to HCV and HCV RNA positive) in the 90 days before enrolment. Patients who had received antiviral or interferon-based treatment for hepatitis C or hepatitis B before enrolment. Patients who had received antiviral or recon

Diagnosis of liver cirrhosis and fatty liver

Cirrhosis was diagnosed by liver biopsy, or Fibroscan (Echosens, Paris, France) score of more than 13 kPa, or radiological image showing nodular liver or splenomegaly combined with platelet count below 100 000. Decompensated cirrhosis was defined as cirrhosis with sequelae such as ascites, variceal bleeding, hepatic
encephalopathy or hepatorenal syndrome. Fatty liver was diagnosed using liver biopsy or hepatic imaging (hepatic ultrasound, CT, MRI).

Data quality control and validation
Peking University People’s Hospital and Bristol-Myers Squibb designed the protocol. All data were inputted into the electronic data capture system at each centre and were examined by one clinical research associate. The contract research organisation controlled and validated the data quality.

Statistical analysis
Data were analysed using SPSS software V.17.0 for Windows. Measurement data were presented as median and IQR (range minimum–maximum) and were examined using the Wilcoxon rank sum test. HCV RNA levels were log-transformed, presented as mean±SD and examined using the Student t test. Categorical variables were expressed as counts and proportions and examined using the χ² test or Fisher’s exact test. Logistic regression analysis was used to identify independent factors associated with HBV/HCV dual infection. p≤0.05 (two-tailed) was considered to indicate significance.

RESULTS
Prevalence of HBV/HCV dual infection in patients with HCV
Basic demographic and clinical characteristics of participants are shown in table 1. The majority were male, with a median age of 46 years (range 18–77) and a mean HCV viral load of 5.83±1.00 log10 IU/mL; 18.56% had cirrhosis. Of the 997 HCV-positive patients, 41 (4.11%) were HBsAg positive (figure 1). HBsAg prevalence by age was 0.70%, 3.97% and 5.85% for age groups 18–30, 30–50 and >50 years old, respectively (p=0.057).

Sociodemographic characteristics and risk factors for HBV/HCV dual infection
The sociodemographic characteristics and risk factors for HBV/HCV dual infection with or without HBsAg are listed in table 2. Subjects with HBV/HCV dual infection were more likely to be older than 30 years (p=0.042, OR=0.162, 95% CI 0.022 to 1.187). Gender, residence in the south of China, a history of blood transfusion and host IL28B genotype were not associated with the presence of HBsAg (p=0.861, p=0.089, p=0.448, p=0.815, respectively).

Clinical characteristics of patients with HBV/HCV and patients with HCV alone
Patients were divided into two subgroups based on their HBsAg status: 41 patients with HBV/HCV dual infection; 956 patients with HCV monoinfection. The clinical characteristics of the two subgroups of patients are listed in table 3. The main path of virus transmission was blood transfusion in both groups. In both groups, the major path of virus transmission for patients with genotype 1 or 2 was blood transfusion, while it was drug injection or other paths for patients with genotype 3 or 6 (24/32 vs 2/9, p=0.006; 526/811 vs 23/145, p<0.000). Biochemical characteristics, including alanine transaminase, aspartate transaminase, total bilirubin, albumin, glutamine transferase, total cholesterol and platelets, were all similar in the two groups.

Virological characteristics of patients with HBV/HCV and patients with HCV alone
Results of HCV RNA and HCV genotype analysis are listed in table 3. The level of serum HCV RNA was 5.80±0.89 log10 IU/mL for the dual-infection group and 5.83±1.00 log10 IU/mL for the HCV monoinfection group (p=0.904).

The main HCV genotype for both groups was 1b, followed by genotypes 2, 3 and 6. Genotypes 4 and 5 were not found. There was no difference in HCV genotypes between the two groups (23/41 vs 559/956, p=0.493). Twenty-one patients (2.1%) were infected with multiple genotypes in the HCV monoinfection group.

Host genotypes of IL28B in patients with HBV/HCV and patients with HCV alone
In this study, 85.36% of patients with dual infection had IL28B genotype CC (rs12979860), while 83.99% of HCV

Table 1 Clinical characteristics of patients

| Characteristic                | Value       |
|------------------------------|-------------|
| Male sex, n (%)              | 546 (54.7)  |
| Mean age, years (range)      | 46 (18–77)  |
| HBsAg positive, n (%)        | 41 (4.11)   |
| Log10 hepatitis C virus RNA, IU/mL (range) | 5.83±1.00 |
| Alanine transaminase, IU/L (range) | 55 (6–1301) |
| Aspartate transaminase, IU/L (range) | 153 (11–541) |
| Cirrhosis, n (%)             | 185 (18.56) |
monoinfected patients had IL28B genotype CC (rs12979860) (p=0.814). The frequency distribution of IL28B host genotypes for the other 12 SNPs based on HBV infection is shown in Table 4. No IL28B host genotypes showed evidence of strong statistical association with HBV/HCV dual infection.

Prevalence of liver cirrhosis and fatty liver in HBV/HCV dual-infected patients

Cirrhosis was reported in 18.56% of all cases. Further analysis showed that 16 of the 41 patients with HBV/HCV (39.02%) and 169 of the 956 patients with HCV (17.68%) had cirrhosis, showing that cirrhosis was more common in patients with HBV/HCV dual infection than in those with HCV monoinfection (13/41 vs 116/956, p=0.001). The prevalence of fatty liver was similar in the two groups (3/41 vs 92/956, p=0.621) (Figure 2).

DISCUSSION

The prevalence of coinfection with HBV and HCV is unknown because of the lack of large-scale studies in China. As HBV and HCV infection are highly endemic, it is essential to investigate the prevalence of HBV/HCV dual infection in China. The epidemiological study performed by Chen et al showed that the anti-HCV positive rate was 14.47% in chronic hepatitis B (CHB) patients. Another study showed that the anti-HCV positive rate was 11.39% among patients infected with HBV in China. However, most information on the prevalence and predictors of HBV/HCV coinfection has
come from studies of populations with chronic HBV infection. There are few data on the prevalence of HBV infection in HCV patients in China where HCV infection is prevalent. Previous studies have shown that 2–10% of patients with HCV might also be infected with HBV in some regions. However, such a conclusion might not be applicable to other countries such as China because the geographic distribution of these two viruses is different and the previous studies were based on either a single centre or preselected patients from several centres. In this study, 4.11% of 997 patients with HCV were also infected with HBV. In our study, all patients with HCV were enrolled during a defined period of time at 28 representative large hospitals in provinces across China. This nationwide, multicentre, large-scale study should well reflect the current prevalence of HBV/HCV dual infection among patients with HCV in China. A recent study by Zhang et al. found that the anti-HCV-positive rate was 3.0% in 227 808 study participants in Northeastern China. Therefore, there are an estimated 30 million individuals with chronic HCV infection in China, and millions of these might also become infected with HBV.

Population-based studies have shown that the prevalence of HBV increases with age. The prevalence in the elderly has been found to be higher than 6%. The prevalence of HBV/HCV dual infection also increases with age. A multivariate analysis demonstrated that HBV/HCV dual infection was independently associated with age. Gender, residence in the south of China, a history of blood transfusion and host IL28B genotype were not associated with the presence of HBsAg.

The main pathway of virus transmission was found to be blood transfusion for both dual infection and HCV monoinfection in this study. Blood transfusion was the leading cause of HCV spread in China because routine HCV screening of blood donors was not introduced until the early nineties. Previous studies have shown that HCV genotype distribution is also associated with the pathway of virus transmission, with subtypes 1a, 3a and 4 being mostly related to intravenous drug use, while genotypes 1b and 2 are associated with blood transfusion and other unsafe medical procedures. Our research showed that the main pathway of virus transmission in patients with genotype 1 or 2 was blood transfusion, while drug injection and other infections were mainly responsible for the spread of genotypes 3 and 6.

Previous studies have shown that HBV and HCV might interact. It has been reported that HCV RNA levels were the same in both patients with HBV/HCV dual infection and those with HCV infection alone. On the other hand, Zarski et al. reported that the HCV RNA level was significantly lower in HBV/HCV patients with

### Table 4: Distribution of host IL28B genotypes in CHC patients according to HBsAg status

| Host genotype IL28B Alleles | HBsAg positive (HBV+HCV) (n=41) | HBsAg negative (HCV) (n=956) | p Value |
|-----------------------------|-------------------------------|-------------------------------|--------|
| rs12979860                  | CC 35 (85.36)                 | 803 (83.99)                   | 0.814  |
|                             | CT/TT 6 (14.63)               | 153 (17.87)                   |        |
| rs8099917                   | TT 35 (85.36)                 | 813 (85.04)                   | 0.955  |
|                             | GT/GG 6 (14.63)               | 143 (15.95)                   |        |
| rs11881222                  | AA 35 (85.36)                 | 796 (83.26)                   | 0.723  |
|                             | GA/GG 6 (14.63)               | 160 (16.73)                   |        |
| rs10853728                  | CC 32 (78.04)                 | 619 (64.75)                   | 0.080  |
|                             | CG/GG 9 (21.95)               | 337 (35.25)                   |        |
| rs28146813                  | GG 6 (14.63)                  | 154 (16.11)                   | 0.801  |
|                             | GC 35 (85.36)                 | 802 (83.89)                   |        |
| rs4803219                   | CC 35 (85.36)                 | 805 (84.21)                   | 0.842  |
|                             | CT 6 (14.63)                  | 151 (15.79)                   |        |
| rs4803223                   | AA 35 (85.36)                 | 802 (83.89)                   | 0.801  |
|                             | GA/GG 6 (14.63)               | 154 (16.11)                   |        |
| rs7248668                   | GG 35 (85.36)                 | 813 (85.04)                   | 0.955  |
|                             | GA/AA 6 (14.63)               | 143 (14.96)                   |        |
| rs12980275                  | AA 34 (82.92)                 | 799 (83.58)                   | 0.912  |
|                             | GA/GG 7 (17.07)               | 157 (16.42)                   |        |
| rs8103142                   | CT 34 (82.92)                 | 758 (79.29)                   | 0.572  |
|                             | TC/CC/TT 7 (17.07)            | 198 (20.71)                   |        |
| rs8105790                   | TT 30 (73.17)                 | 675 (70.61)                   | 0.724  |
|                             | TC/CC 11 (26.83)              | 281 (29.39)                   |        |
| rs8109886                   | CC 35 (85.36)                 | 773 (80.86)                   | 0.471  |
|                             | CA/AA 6 (14.63)               | 183 (19.14)                   |        |
| rs10853727                  | TT 41 (100)                   | 947 (99.06)                   | 0.533  |
|                             | TC 0 (0.00)                   | 9 (0.94)                      |        |

Values are n (%). HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; CHC, chronic hepatitis C.
positive HBV DNA than in HBV/HCV patients with negative HBV DNA. In this study, we found similar HCV RNA levels in patients with dual HBV/HCV infection or HCV monoinfection. Owing to the lack of HBV DNA data, we did not perform statistical analysis on stratified groups based on HBV DNA. The observed disparities may be accounted for by the huge statistical difference between the stratified groups based on HBV DNA data.

A systematic review of HCV genotypes in China showed that the main ones are 1b and 2a subtypes.\textsuperscript{19} In this study, we found that the prevailing HCV genotype was still 1b in both HBV/HCV patients and HCV patients, followed by genotypes 2, 3 and 6, in agreement with previous reports.\textsuperscript{21}

The prevalence of IL28B rs12979860 CC genotypes was similar in both HBV/HCV dual-infected patients and HCV monoinfected patients (85.36% vs 83.99%, p=0.814). In China, the high frequency of the IL28B C allele (rs12979860) in both dual-infected patients and HCV monoinfected patients may contribute to the high rate of sustained virological response (SVR) to peginterferon plus ribavirin treatment.\textsuperscript{22–24} Direct-acting antivirals (DAAs) are gradually becoming the major therapy. Overall SVR rates of DAAs were above 90% in numerous patient cohorts. Overall SVRs of ledipasvir and sofosbuvir were above 90% for untreated patients with HCV genotype 1 infection, most with a non-CC IL-28B genotype.\textsuperscript{25} Other studies have shown that patients with genotypes 4 and 5 who did not achieve SVR12 to ledipasvir and sofosbuvir treatments had non-CC IL-28B genotype.\textsuperscript{26,27} A randomised head-to-head study is needed to explore the effect of IL-28B on DAA treatment. This study laid the foundation for future research in this field.

It has been suggested that HBV/HCV dual infection has a more severe evolution in the long term than HBV or HCV monoinfection.\textsuperscript{10,28} In addition, several cross-sectional studies found that dual infection is associated with a higher risk of liver cirrhosis and hepatic decompensation compared with HBV or HCV monoinfection,\textsuperscript{6,29} without a broadly represented population. It should be emphasised that HBV/HCV dual-infected patients are an extremely heterogeneous population. Most clinical studies performed so far did not examine extensively viral and host properties. In this study, the epidemiological, biological and virological characteristics and the host IL28B genotypes of dual-infected patients were mostly in line with those of HCV monoinfected patients. Our research also confirmed that HBV/HCV dual infection was significantly associated with a higher risk of liver cirrhosis and hepatic decompensation than HCV monoinfection (39.02% vs 17.69%, p=0.001; 31.70% vs 12.13%, p=0.001). Therefore, HBV/HCV dual infection might be the predominant cause of cirrhosis. Since cirrhosis is more severe in patients with HBV/HCV dual infection, frequent monitoring of cirrhosis would lead to an earlier diagnosis, better management and prevention of hepatocellular carcinoma. However, owing to the poor economic conditions and low social status of most patients with HBV/HCV, the diagnosis of hepatitis and cirrhosis was always delayed, leading to delay in treatment. Therefore, patients with HBV/HCV dual infection need more attention from medical professionals to ensure timely and effective treatment.

There are several limitations of this study. First, HBV viral load was not measured because of the shortage of serum in the dual infection group. Viral interactions between HBV and HCV need to be further explored. No data on occult HBV were available because HBV DNA analysis was not performed. This may have led to underestimation of the real burden of HBV in this study population.\textsuperscript{30} Second, no sequencing of HBV genes was carried out, which could have provided insights into molecular epidemiology, escape mutations and drug-resistance variants in this study population. No quantitative measurement of HBsAg was performed, which could have provided insights into the covalently closed circular DNA metabolic effect at the liver level.\textsuperscript{31} Third, a prospective study with an adequate follow-up period is needed to investigate the role of HBV infection in the outcome of HCV infection. Last, information
about transmission was obtained by interview, thus recall bias is inevitable. Further study is needed to access the treatment response of HBV/HCV dual-infected patients to either peginterferon/ribavirin or other direct-acting antiviral agents.

In conclusion, this nationwide, multicentre, large-scale population-based study indicates that the prevalence of HBV/HCV dual infection in patients with HCV is 4.11%. The HBV burden was moderate among HCV-infected patients in China. Liver cirrhosis was more common in patients with HBV/HCV dual infection than in patients with HCV monoinfection, suggesting a need for closer monitoring of dual-infected individuals.

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Acknowledgements We appreciate Professor Jia Shang in Henan Provincial People’s Hospital, Professor Hong Chen in First Hospital of Lanzhou University, Professor Jun Li in First Affiliated Hospital with Nanjing Medical University, Professor Qing Xie in Shanghai Ruijin Hospital, Professor Zhiliang Gao in Third Affiliated Hospital of Sun Yat-sen University, Professor Lei Wang in Second Hospital of Shangdong University, Professor Jia Wei in First Affiliated Hospital of Kunming Medical College, Professor Jianning Jiang in Second Hospital of Shangdong University, Professor Jia Wei in First Affiliated Hospital of Anhui Medical University, Professor Jian Sun in Second Hospital of Harbin, Professor Shaofeng Wei in Southwest Hospital of China Medical University, Professor Junqi Niu in First Affiliated Hospital of Nanchang University, Professor Longfeng Zhao in First Affiliated Hospital of Shaxi Medical University, Professor Xiaoguang Dou in Shengjing Hospital of China Medical University, Professor Junqiu Niu in First Hospital of Jilin University, Professor Hong You in Beijing Friendship Hospital, Capital Medical University, Professor Zhi Chen in First Affiliated Hospital of Medical College Zhjia Jiang University, Professor Qin Ning in Affiliated Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Professor Guozhong Gao in Second Xiangya Hospital of Central South University, Professor Shuhsan Wu in First Affiliated Hospital of Zhengzhou University, Professor Wei Ji in Ningxia People’s Hospital, Professor Qing Hao in Southwest Hospital, Professor Shuchen Li in Second Affiliated Hospital of Harbin, Professor Shaoqiong Wei in First Affiliated Hospital of Anhui Medical University, Professor Jian Sun in Nanyang Hospital, Southern Medical University, Professor Jiayi Ji in First Affiliated Hospital of Fujian Medical University, Professor Lungen Lu in Shanghai First People’s Hospital, Shanghai Jiao Tong University School of Medicine, Professor Hui Zhaung in Peking University Health Science Center for their contribution to this work.

Contributors LW and HT conceived the study, provided funding and revised the manuscript critically for important intellectual content. L-BY, H-YR and Y-JM made substantial contributions to data collection. E-QQ, LB and L-YD conducted data analysis. L-BY and R-F-Y participated in interpretation of data and manuscript preparation. L-BY drafted the manuscript and revised it according to all the authors’ opinions. All authors have read and approved the final manuscript.

Funding This work was supported by grants from the China National Science and Technology Major Project for Infectious Diseases Control during the 12th Five-Year Plan Period (grant number2012ZX10002007-001-003, 2012ZX10002003 and 2012ZX10002005) and from Bristol-Myers Squibb.

Competing interests None declared.

Ethics approval This study was approved by the ethics committee of 28 university-affiliated hospitals.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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REFERENCES

1. Sotgiu G, Altrafi I, Razavi HA, et al. A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt. Liver Int 2011;31 (Suppl 2):61–80.
2. Saravanan S, Velu V, Nandakumar S, et al. Hepatitis B virus and hepatitis C virus dual infection among patients with chronic liver disease. J Microbiol Immunol Infect 2009;42:517–20.
3. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661–2.
4. European Association for Study of Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. J Hepatol 2014;60:392–420.
5. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5:558–67.
6. Caccamo G, Saffo F, Raimondo G. Hepatitis B virus and hepatitis C virus dual infection. World J Gastroenterol 2014;20:14559–67.
7. Tyson GL, Kramer JR, Duan Z, et al. Prevalence and predictors of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients. Hepatology 2013;58:538–45.
8. Bini EJ. Perumalswami PV. Hepatitis B virus infection among American patients with chronic hepatitis C virus infection: prevalence, racial/ethnic differences, and viral interactions. Hepatology 2010;51:759–66.
9. Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. J Gastroenterol Hepatol 2009;24:512–20.
10. Zarksi JP, Bohn B, Bastle A, et al. Characteristics of patients with dual infection by hepatitis B and C viruses. J Hepatol 1998;28:27–33.
11. Liu CJ, Chen PJ, Chen DS. Dual chronic hepatitis B virus and hepatitis C virus infection. J Microbiol Immunol Infect 2009;42:517–20.
12. Rao H, Wei L, Lopez-Talavera JC, et al. Distribution and clinical correlates of viral and host genotypes in Chinese patients with chronic hepatitis C virus infection. J Gastroenterol Hepatol 2014;29:545–53.
13. Chen X, Xuan M, Wu D. [Study of superinfection of HBV and HCV]. Zhonghua Liu Xing Bing Xue Za Zhi 1999;20:141–3.
14. Li W, Zhu Y, Hua Z. [Exploration on the association between the pattern of HBV markers and infection of HCV among population]. Zhonghua Liu Xing Bing Xue Za Zhi 1994;15:212–14.
15. Zhang G, Qi W, Wang X, et al. Epidemiology of hepatitis B and hepatitis C infections and benefits of programs for hepatitis prevention in northeastern China: a cross-sectional study. Clin Infect Dis 2016;62:305–12.
16. Gower E, Estes C, Blach S, et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014;61:545–77.
17. Esteban JI, Saulea S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol 2008;48:148–62.
18. Pawlotsky JM, Tsakiris L, Roudot-Thoraval F, et al. Relationship between hepatitis C virus genotypes and sources of infection in patients with chronic hepatitis C virus. J Infect Dis 1995;171:1607–10.
19. Cui Y, Jia J. Update on epidemiology of hepatitis B and C in China. J Gastroenterol Hepatol 2013;28(Suppl 1):7–10.
20. Su YY, Liu HX, Wang N. [Hepatitis C virus genotypes in China: a systematic review]. Zhonghua Liu Xing Bing Xue Za Zhi 2013;34:80–4.
21. Lu L, Nakano T, He Y, et al. Hepatitis C virus genotype distribution in China: predominance of closely related subtype 1b isolates and existence of new genotype 6 variants. J Med Virol 2005;75:539–49.
22. Dong ZX, Zhou HJ, Xiang XG, et al. IL28B genetic variants are associated with treatment response of patients with chronic hepatitis C in a Chinese Han population. J Dig Dis 2015;16:90–7.
23. Mi Y, Gao YT, Xiao XL, et al. The role of interleukin-28b gene polymorphisms in Chinese patients with chronic hepatitis C treated with pegylated interferon and ribavirin. Hepat Mon 2014;14:e18793.
24. Liao XW, Ling Y, Li XH, et al. Association of genetic variation in IL28B with hepatitis C treatment-induced viral clearance in the Chinese Han population. Antivir Ther 2011;16:141–7.

25. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014;370:1889–98.

26. Abergel A, Asselah T, Metivier S, et al. Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. Lancet Infect Dis 2016;16:459–64.

27. Abergel A, Metivier S, Samuel D, et al. Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection. Hepatology 2016;64:1049–56.

28. Sagnelli E, Pasquale G, Coppola N, et al. Influence of chronic coinfection with hepatitis B and C virus on liver histology. Infection 2004;32:144–8.

29. Villari D, Pernice M, Spinella S, et al. Chronic hepatitis in patients with active hepatitis B virus and hepatitis C virus combined infections: a histological study. Am J Gastroenterol 1995;90:955–8.

30. Coppola N, Onorato L, Pisaturo M, et al. Role of occult hepatitis B virus infection in chronic hepatitis C. World J Gastroenterol 2015;21:11931–40.

31. Xie Q, Jiang X, Zhang Y, et al. Intrahepatic hepatitis B virus covalently closed circular DNA correlation with serum HBV DNA, serum HBsAg, alanine aminotransferase and age. Zhonghua Gan Zang Bing Za Zhi 2015;23:418–21.