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REVIEW
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Prevalence, diagnosis, and treatment of hepatitis C in Mainland China

Xue Mei[1], Hongzhou Lu[2,*]

[1] Department of Severe Hepatology, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China;
[2] Department of Infections Disease, Shenzhen Third People's Hospital, Shenzhen, China.

Abstract: Infection with the hepatitis C virus (HCV) is a major cause of liver disease and hepatocellular carcinoma in China. Rapid economic development has had an enormous impact on the epidemiology and treatment of hepatitis C. The prevalence of anti-HCV antibodies in Mainland China is approximately 0.91%, and use of injected drugs has become the main route of HCV transmission in China. Reimbursement for 3 direct-acting antivirals (DAAs) has been approved by the National Medical Insurance scheme in China, which ensures the accessibility of treatment for an HCV infection. To improve the awareness of treatments for hepatitis C among medical personnel and the rate of in-hospital screening for HCV, the Chinese Medical Association has formulated guidelines for the diagnosis and treatment of hepatitis C and a process of in-hospital screening for hepatitis C in China. These efforts have standardized the screening, diagnosis, treatment, and management of hepatitis C. Based on the international strategy for micro-elimination of hepatitis C, China has also screened and treated groups at risk of hepatitis C infection, and this has reduced the number of the infected. The current review describes the status of and issues with the prevalence, diagnosis, and treatment of hepatitis C in Mainland China as part of the global effort to eliminate viral hepatitis by 2030.

***Keywords*:** prevalence, diagnosis, treatment, hepatitis C, Mainland China

Introduction

In 2016, the World Health Organization (WHO) proposed a new global goal to eliminate viral hepatitis by 2030 (*1*). Compared to 2015, the incidence of hepatitis C decreased by 80% and its mortality decreased by 65%, and 90% of patients with hepatitis C were diagnosed and 80% of eligible patients were treated (*1,2*). The Chinese Government and healthcare system are tirelessly working to achieve the goal of eliminating hepatitis C as soon as possible. There are approximately 10 million patients infected with the hepatitis C virus (HCV) in China, and they account for more than 14% of the global population infected with HCV (*3*). Nearly one-fifth of the total deaths from hepatitis C-related cirrhosis and hepatocellular carcinoma occur in China every year (*1*).

Current data on hepatitis C in China indicate that the number of patients with hepatitis C-related cirrhosis or liver cancer and deaths from those conditions will increase over the next 12 years (*3*). This will increase the disease burden for patients, society, and the medical system. The current status of hepatitis C in China needs to be promptly ascertained in order to reduce the burden of HCV infection and achieve the goal of eliminating hepatitis C by 2030.

Discussed here are the status of and issues with the epidemiology, diagnosis, and treatment of and screening for hepatitis C in Mainland China.

Epidemiological changes

Chronic hepatitis C is a substantial medical burden worldwide. China has one of the world's largest populations with hepatitis C. In China, there are about 200,000 new cases of hepatitis C and 360,000 liver cancer deaths every year in which liver cancer-associated with hepatitis C accounts for 37.48%. There are at least 133,000 deaths caused by hepatitis C (*3-5*).

Over the past 30 years, the prevalence of anti-HCV antibodies has changed in Mainland China (Figure 1). A study conducted in 1992 found that the prevalence of anti-HCV antibodies was 3.2% (*6*). China subsequently took effective measures to prevent the spread of HCV infection, blood donation was changed from paid to voluntary, and disinfection standards and hospital infection control standards were implemented (*7,8*). The prevalence of anti-HCV antibodies in China had dropped to 0.43% by 2006 (*9*). However, the prevalence of anti-HCV antibodies (0.58%) increased from 2011 to 2015, which may be related to the enhancement of hepatitis C screening and the variety of routes of HCV infection in recent years (*10*). A recent meta-analysis reported that the

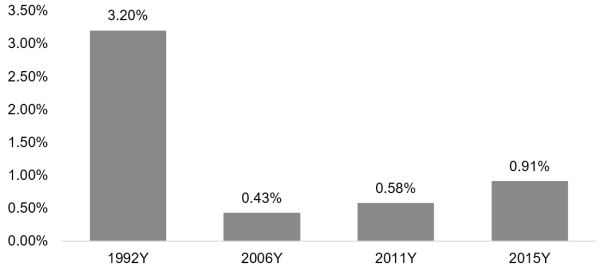

Figure 1. Changes in levels of anti-HCV antibodies in Mainland China.

prevalence of anti-HCV antibodies in Mainland China is 0.91% [95% confidence interval (CI) 0.81-1.03%] (*10*). The prevalence of anti-HCV antibodies differed significantly in different regions, ranging from 0.32% to 6.51%, and the rate of detection was relatively low in East China and South China (*9,10*). The prevalence of anti-HCV antibodies in rural areas seems to be higher than that in urban areas, which may be related to poor medical conditions and less health awareness (*11*). As age increased, the rate of detection of anti-HCV antibodies increased from 0.16% to 3.95% (*10,12*).

There are eight HCV genotypes (GT1-8) reported around the world, and GT1-6 is found in China (*13,14*). GT1b and GT2a are the main genotypes of HCV in China, accounting for 62.78% (95% CI: 59.54-66.02%) and 17.39% (95% CI: 15.67-19.11%), respectively. The prevalence of HCV-GT differs markedly among regions. In northern and central China, GT1b and GT2a still are the main subtypes (*15,16*). However, the genotypes distribution in southern China is transitioning from GT1b to GT3 and GT6; about half of the population infected with HCV in southern China have the GT1b genotype, and more than 40% of the population have GT3 or GT6 (*14,17*). These marked changes may be related to population mobility and use of addictive intravenous drugs as a route of transmission. In recent years, the proportion of co-infection with multiple HCV subtypes in China has gradually increased, and these subtypes are mainly GT1b, GT2a, and GT6a (*14,18*). The most common is co-infection with GT1b/2a, which accounts for 81.8%, followed by co-infection with GT6a/2a and GT6a/1a (*14,19*). Co-infection with multiple HCV subtypes is mainly found in patients who repeatedly received blood products, shared needles with intravenous drug users, or who often underwent hemodialysis (*14,20*).

Changes in the routes of HCV transmission

Due to lack of supervision of the safety of blood products in the past, the main route of HCV infection in China was through blood transfusions (*20*). In 1993, the Chinese Government formulated a policy to screen blood donors and it enacted related laws to screen all blood donors for anti-HCV antibodies. Since 2015, China began to screen blood donors who were anti-HCV antibody-negative for HCV RNA. In addition, the methods of recruiting blood donors have gradually changed (*21*). Apart from these, the standards for disinfection, nosocomial infection control standards, and hepatitis C prevention and control guidelines have been formulated and put into practice. These measures significantly reduced the spread of HCV infection. Since then, HCV infection by blood transfusion has rarely occurred. The main high-risk population has gradually become patients who inject drugs (PWID), patients undergoing hemodialysis (HD), and patients co-infected with the human immunodeficiency virus (HIV), or patients infected with the hepatitis B virus (HBV) (*22*).

At present, use of injected drugs has become the main route of HCV transmission in China. Infection with HCV through unsafe injections accounts for 30-49% of all infections, and the figure is as high as 60-90% in some provinces (*10,22*). In Hubei, Yunnan, Guangxi, Hunan, and Xinjiang, the prevalence of HCV was the most serious among PWIDs (*22*). In a study of more than 2,000 PWIDs in Yunnan Province, 77% of the participants were infected with HCV (*23*). Due to needle sharing, the prevalence of HCV among injected drug users in China is higher than that among general drug users, including those who take drugs oral or *via* inhalation (80.0%) and those who voluntarily or compulsorily recover or receive methadone maintenance treatment) (48.7%) (*22,24*). The prevalence of HCV is about 5.21-8.25%, and the figure is as high as 30.2-38.1% in some dialysis units (*22,25*).

High-risk sexual behavior is also one of the main routes for HCV transmission among patients infected with HIV. Several studies have indicated that the incidence of HCV infection among people infected with HIV in China ranges from 8% to 18% (*26,27*). In addition, sharing of razors in households, unsafe ear piercings, and tattoos may also lead to HCV infection. Mother-to-child transmission is also a common route of HCV infection. According to one study, pregnant women on the Chinese Mainland tested positive for anti-HCV antibodies at a rate of 0.235%, the incidence of HCV transmitted to newborns by HCV-positive mothers is about 2% (*28*). A high HCV RNA load and HIV infection can increase the risk of transmission.

Status of diagnosis and detection

Studies have indicated that the rate of diagnosis of hepatitis C in China is only 2.1% (*8,29*). Early screening and diagnosis are always the biggest obstacles to eliminating infection with HCV. At present, the methods of detecting HCV infection in China include serological detection (detection of anti-HCV antibodies or the HCV core antigen) and detection of nucleic acids (HCV RNA) (*30*). Hospitals and communities mainly screen for HCV infection *via* serum anti-HCV antibodies. Patients who are positive for anti-HCV antibodies are commonly tested for HCV RNA to determine whether they are currently infectious or not. Due to its low specificity and

sensitivity, HCV core antigen detection is not widely used (*31*).

However, some researchers have recently proposed an assessment involving the simultaneous detection of the HCV core antigen and HCV non-structural proteins. Compared to serum anti HCV antibody detection and HCV-RNA detection, detection of multiple HCV antigens has a specificity of 98.9% and a sensitivity of 100% (*32*). A recent study has reported an immunoassay to detect the HCV core protein in antibody-negative samples during the early stage of HCV infection (*32*). This method is well-suited to screening blood products in blood banks for HCV and monitoring the HCV viral load after liver transplantation, and it is especially useful at screening when detection of HCV RNA is difficult.

The 2019 Chinese guidelines for prevention and treatment of hepatitis C state that the HCV core antigen is a marker of HCV replication and could replace HCV RNA in the diagnosis of an acute/chronic HCV infection. HCV core antigen detection could be used when detection of HCV RNA is not feasible (*8*).

Changes in treatment: From PR to DAA

Although 25% of China's 10 million patients with chronic hepatitis C need urgent treatment, less than 1.3% receive treatment (*33*). Prior to 2017, treatment for hepatitis C mainly involved interferon and ribavirin (PEG/RBV) for 24 or 48 weeks based on the genotype (*34*). Treatment is expensive, its efficacy is only 60-70%, some patients had adverse reactions, and the treatment takes a long time (*35*). Many patients often discontinue treatment for economic reasons. Since 2017, China's health authorities have made substantial progress in the prevention and treatment of hepatitis C. Several direct-acting antivirals (DAAs) have been approved for marketing in China. After oral administration for 8–16 weeks, a sustained virological response (SVR) has been achieved in more than 90% of patients infected with any genotype of HCV, adverse reactions are rare, and patient tolerance and compliance are better (*36*).

In 2019, the Chinese Medical Association updated its guidelines on hepatitis C to keep pace with international standards (*8*). The guidelines indicate that DAAs could replace the conventional regimen of interferon combined with ribavirin and that DAAs become the first-line therapy for hepatitis C, further standardizing the treatment of hepatitis C in China. Three DAAs for hepatitis C were subsequently included in the list of medications reimbursed by medical insurance, with an average price reduction of more than 85% (*37*). This changed the situation for patients who discontinued treatment because of its expense. Two of the medications, elbasvir/grazoprevir and ledipasvir/sofosbuvir, are for patients with GT1b hepatitis C. A third medication is sofosbuvir/velpatasvir (SOF/VEL). The simplified regimen of SOF/VEL for 12 weeks could meet the clinical needs of most patients infected with HCV, including patients with chronic kidney disease, decompensated cirrhosis, and previous treatment failure. SOF/VEL is highly efficacious in and well tolerated by patients with any of the six HCV genotypes (GT1-6) and in different stages of liver fibrosis in China. There is no need to detect the HCV genotype or the stage of fibrosis before treatment, and no dynamic monitoring is required during therapy (*8*). Clinical use is convenient and feasible, further reducing medical expenses and potentially improving the rate of compliance in rural areas.

In addition, the first-line salvage therapy recommended by the HCV guidelines is Vosevi tablets (sofosbuvir, velpatasvir, and voxilaprevir tablets) (*38*). This medication was also approved for reimbursement by medical insurance in December 2019, providing treatment options to patients with hepatitis C in whom previous DAA treatment failed. Clinical studies have indicated that Vosevi had an overall cure rate of 97% in patients who failed to respond to DAA treatment, regardless of the state of liver cirrhosis and the DAAs that they had previously received. In addition, China has also independently developed some DAAs. Phase II-III clinical trials of the DAAs Ganovo (danoprevir or ASC08) and ravidasvir (a next-generation NS5A inhibitor of all genotypes) were completed in June 2018. Ravidasvir and danoprevir are the first oral interferon-free regimen developed in China. The regimen achieved an SVR of 99% at 12 weeks in non-cirrhotic GT1 patients receiving initial treatment and an SVR of 100% in patients with NS5A resistance mutations at the baseline. In July 2020, China approved the 2 drugs for use in combination with other drugs in non-cirrhotic GT1 patients (*39*). The approval of domestic DAAs in China could reduce medical costs and make drugs more accessible to patients infected with HCV. These efforts have improved the diagnosis and treatment of hepatitis C in China and they represent a step towards achieving the global goal of "eliminating viral hepatitis by 2030".

Improved screening

As DAAs have become more available, the treatment of hepatitis C in China has become more feasible. The key lies in screening for the infected. A study analyzed the detection and prevalence of anti--HCV antibodies in inpatients at 8 tertiary hospitals in different regions of China from January to December 2016 (*40*). Results indicated that the rate of detection of anti-HCV antibodies was no higher than 50% and average positivity was 0.88%; results also indicated that 90.14% of anti-HCV antibody-positive patients were over 40 years old. Due to a lack of consultation and referral for diagnosis and treatment, anti-HCV antibody-positive patients often have no chance to receive early treatment. A 2016 to 2018 study of patients infected with HCV at

76 hospitals in China found that the rate of detection of anti-HCV antibodies was 48.4%, while the rate of detection of HCV RNA was 34.9%; the missed diagnosis rate was as high as 65.1%, resulting in only 12.2% of the population receiving antiviral treatment (*41*).

Clinicians in Non-infectious Liver Diseases have a limited awareness of hepatitis C, and especially the need for hepatitis C screening and standards for diagnosis, treatment, and management of hepatitis C. Moreover, patients with obvious clinical manifestations of chronic viral hepatitis and a high risk of infection with HCV lack awareness of active testing (*42*). Thus, the Chinese Medical Association formulated its "process of in-hospital screening for hepatitis C in China" in 2021 (*43*). The process recommends creation of a multidisciplinary team (MDT) and it recommends that clinical departments, the laboratory, and infection control at medical facilities enhance the referral and treatment of anti-HCV antibody-positive patients and promote the screening/diagnosis and antiviral treatment of patients with chronic hepatitis C (Figure 2).

Recently, the European Association for the Study of the Liver (ESAL) proposed a more pragmatic strategy – "Conquering Hepatitis C *via* Micro-Elimination (CHIME)" (*44*). This approach breaks down the goal of eliminating hepatitis C into providing interventions for specific groups (such as high-risk groups), including marginalized groups (such as PWIDs). As an example, screening high-risk groups is more effective than screening the general population. Efficacious DAAs can also be prioritized for treatment of these high-risk groups, which may reduce the spread of the disease to the general population.

Given its population and socio-economic conditions, China is also optimizing the micro elimination strategy in different regions. At present, potential target populations for the HCV micro elimination strategy in China are PWIDs, patients undergoing HD, patients co-infected with HIV, women of childbearing age, pregnant women, and children. In early 2018, an assistance program to identify and treat hepatitis C initiated by the Primary Healthcare Foundation of China was rolled out to the entire country (*45*). The program provides free medication for patients with the lowest standard of living and half-price medication for low-income patients. These initiatives are moving in the right direction and are helping to improve the management of hepatitis C (Figure 3).

Recently, AI and information technology and efforts to identify patients *via* their medical data have gradually been used in China. Although action is being taken, problems with the management of HCV, such as a lack of general awareness of hepatitis C, a low screening rate, and poor ties to medical care, have not been completely resolved in China. In the future, the current prevention and control strategies need to be further optimized and coordination among public health departments, Centers for Disease Control, and tertiary medical facilities needs to be enhanced. Promoting more cost-effective screening and treatment of HCV infection in the population could

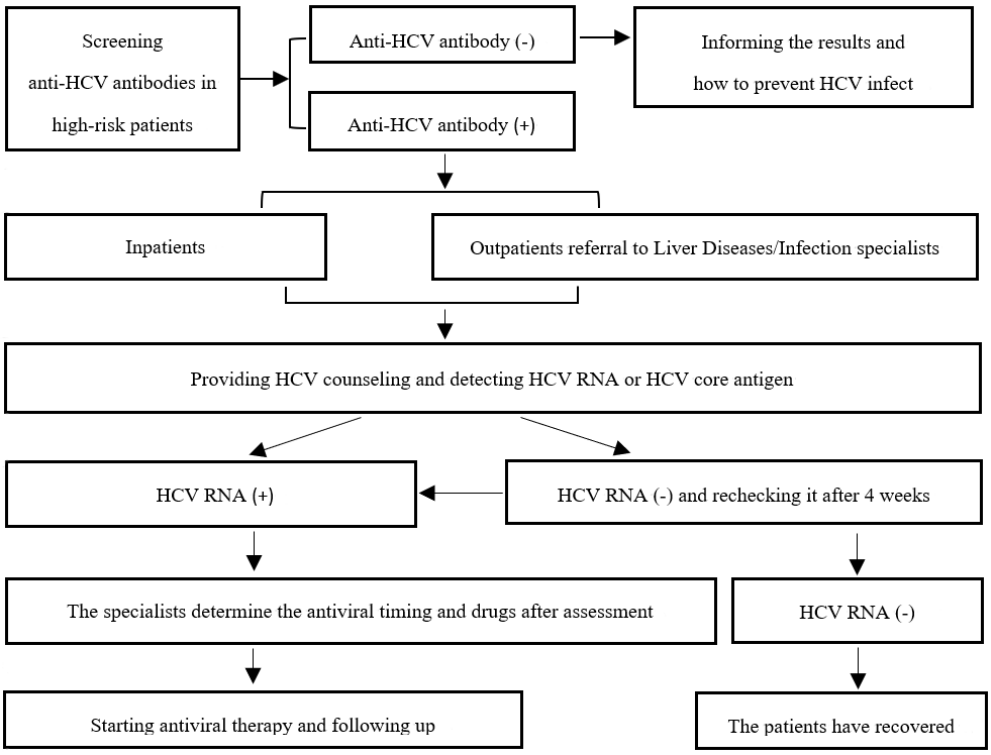

Figure 2. Flow chart for the process of in-hospital screening for hepatitis C in China. *Abbreviations*: HCV, hepatitis C virus; (+), positive; (-), negative.

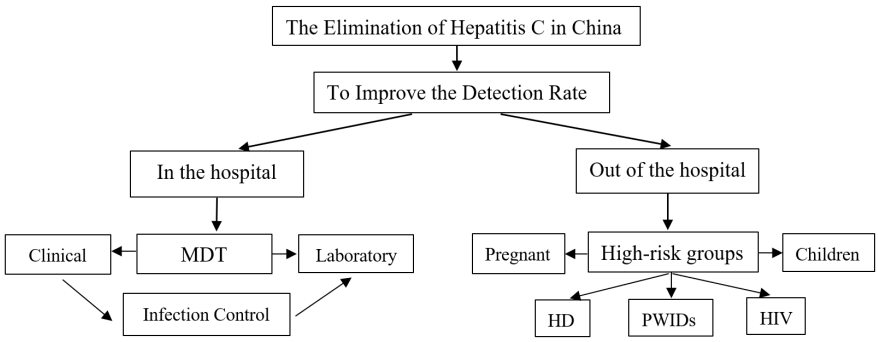

Figure 3. The elimination of hepatitis C in China. *Abbreviations:* MDT, multidisciplinary team; HD, hemodialysis; PWID, patients who inject drugs; HIV, human immunodeficiency virus.

lead to the successful elimination of hepatitis C in China by 2030.

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**Address correspondence to*:
Hongzhou Lu, Department of Infections Disease, Shenzhen Third People's Hospital, No. 29, Bulan Road, Longgang District, Shenzhen, Guangdong Province 518112. China.
E-mail: luhongzhou@fudan.edu.cn