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Incidence trend and age-period-cohort analysis of reported hepatitis C among residents aged 30 to 79 in northeastern China, 2008 to 2017

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Abstract

The purpose of this study was to acquire the epidemic trend of age-standardized reported incidence and to analyze the age effect, period effect, and cohort effect on the reported incidence of hepatitis C in Jilin Province, China.

We collected the annual reported incidence data of hepatitis C by gender (2008–2017). Annual percentage change and annual average percentage change were calculated by joinpoint Poisson regression analysis. The age effect, period effect, and cohort effect on the incidence of hepatitis C were estimated by an age-period-cohort model, and the relative risk was determined.

Joinpoint regression analysis showed that the age-standardized reported incidence of hepatitis C indicated a declining trend integrally. Among people aged 30 to 44 (youth), the incidence trend declined the fastest, while trends declined the slowest among women and the overall population aged over 66 (elderly people) and men aged 45 to 65 (middle-aged group). The results of the age-period-cohort model showed that the reported incidence increased first and then decreased with age. Throughout the period, the risk of hepatitis C also increased first and then decreased. Compared with the median birth cohort of the same age group, the birth cohort of the patients with the highest incidence of hepatitis C was in the 1930s, followed by the 1940s and 1950s. The birth cohort of the patients with the lowest incidence was in the 1980s, followed by the 1970s and 1960s.

Although the overall reported incidence trend of hepatitis C is declining and the risk of the young birth cohort is low, many factors affecting infection and testing with hepatitis C still exist in China. We should focus on high-risk population management and formulate corresponding public health strategies to accelerate the implementation of the global health strategy to eliminate hepatitis C published by the World Health Organization.

Abbreviations: AAPC = average annual percentage change, APC = annual percentage change, HCV = hepatitis C virus.

Keywords: age-period-cohort analysis, hepatitis C, joinpoint regression analysis

1. Introduction

Hepatitis C is one of the leading risk factors for cirrhosis and liver cancer. It is estimated that approximately one-third of hepatocellular carcinoma cases worldwide can be attributed to hepatitis C virus infection,[1] and hepatitis C has become the second-highest disease burden of liver cancer in China.[2] Globally, the infection rate of hepatitis C virus is ~3%, with 184 million cases, and ~399 thousand people die of hepatitis C every year.[3–5] The prevalence of hepatitis C is 2.8%, while the viraemic rate is 63.6% in China (including Taiwan).[6,7] Previous studies have reported that the widespread incidence of hepatitis C is related to blood transfusion and injection drug abuse, and the incidence of hepatitis C caused by opioid abuse is also on the rise.[8] The treatment of hepatitis C has been significantly improved due to the strategy of eliminating hepatitis C virus infection in 2030 proposed by the World Health Organization and the application of direct-acting antiviral agents treatment. However, at present, because the diagnostic rate of hepatitis C is <20%, and only <10% of patients have received antiviral and adjuvant treatment, hepatitis C remains a serious global public health challenge.[9–11] Too little work has been devoted to the temporal trend of hepatitis C incidence in China. Especially with the

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QZ and SJ contributed equally to this work.

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The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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rapid economic development and the improvement of public health policies in China, all these changes may have varying degrees of effects on the reported incidence of hepatitis C in different age groups, different periods, and different birth cohorts. Therefore, we can better identify the type of population with the highest risk by closely assessing the characteristic population of infected individuals. This study provides new insights into identifying the pattern of hepatitis C by using an age-period-cohort model to analyze the trend of age-standardized reported incidence in Jilin Province, China, 2008 to 2017. Then, according to the epidemiological changes over the years, appropriate public health policies for hepatitis C can be formulated.

2. Materials and methods

2.1. Study area

Jilin Province lies in the central part of northeast China, located between latitude 40°50' to 46°19' north and longitude 121°38' to 131°19' east, with a total area of 18.74 thousand square kilometers. There are eight cities, one prefecture, and 27.04 million permanent residents (at the end of 2018).

2.2. Ethical standards

This study was approved by the Ethics Committee of the Jilin Center for Disease Control and Prevention, and the requirement for ethical approval for this study was waived.

2.3. Data source

Hepatitis C is a Class B notifiable infectious disease in China. We obtained data from the Jilin Notifiable Disease Surveillance System, which is a part of the China Disease Prevention and Control Information System (http://www.jlqx.gov.cn/). The doctor diagnoses the patient on the basis of the diagnostic criteria for hepatitis C (see Supplemental Table 1, Supplemental Content, which demonstrates the diagnostic criteria for hepatitis C by the law on the prevention and control of infectious diseases of the People's Republic of China, http://links.lww.com/MD/E801). Combined with the epidemiological history, clinical symptoms, and laboratory test results, the "Infectious Disease Report Card of the People's Republic of China" is completed (see Supplemental Table 2, Supplemental Content, which illustrates infectious disease report card of the People's Republic of China, http://links.lww.com/MD/E802). The report card is uploaded to the Jilin Notifiable Disease Surveillance System within 24 h. The Jilin Center for Disease Control and Prevention will check, review, and correct the reported information. All recorded cases in the Jilin Notifiable Disease Surveillance System are newly diagnosed and not newly infected. Therefore, the incidence shown in this study represents the reported incidence. Data on the reported incidence of hepatitis C among permanent residents in Jilin Province (including eight cities and one prefecture) from 2008 to 2017 were collected. The study variables included birth date, sex, diagnostic results and dates of onset and diagnosis, all recorded anonymously. Population data were obtained from the Basic Information System for China Disease Prevention and Control and China Statistical Yearbook. Age-standardized reported incidences were calculated per 100,000 individuals by using population estimates based on the 2010 census of China as the standard population.

2.4. Statistical analysis

The data on the reported incidence of hepatitis C among adults aged 30 to 79 years from 2008 to 2017 were selected for analysis. We used R software (version 3.5.3; http://www.r-project.org) to calculate the age-standardized reported incidence of hepatitis C in males, females and the overall population and drew age-specific, period-specific and cohort-specific incidence figures to observe the reported incidence of hepatitis C in Jilin Province.

We used Joinpoint Regression Software (version 4.7.0.0), developed by the National Cancer Institute, for joinpoint regression analysis.[12] We fitted the reported incidence of hepatitis C to a log-linear model (based on the Poisson distribution) and used a Monte Carlo permutation test to determine the number of joinpoints, the location of each joinpoint and the *P* value. The best model was selected according to the Bayesian information criterion. Then, the annual percentage change (APC), average annual percentage change (AAPC) and their 95% confidence intervals were calculated to reveal the time trend of the reported incidence of hepatitis C in Jilin Province. The age groups were as follows: a 30- to 44-year-old group (youth), a 45- to 65-year-old group (middle-aged people), and a 66- to 79-year-old group (elderly people).

Using the APCfit command in Stata (version 12.1), we used the age-period-cohort model to analyze different gender groups based on the cubic spline parametric smoothing function and estimated reported incidence and incidence rate ratios of hepatitis C using 5 knots for age, period, and cohort variables.[13] The principle of the age-period-cohort model was to use a generalized linear Poisson regression model to analyze the influence of age, period, and cohort on the reported incidence of hepatitis C in different sex groups by matrix transformations. The model eliminated the problem of overparameterization (cohort = period-age) and the exclusion of one factor. The age effect could show the specific incidence of different age groups; the period effect provided the impact of diagnosis and treatment on all age groups, while the cohort effect was the result of historical exposure. Using the median birth cohort as a reference cohort and adjusting for the effects of age and period factors, incidence rate ratios were used to describe the independent risk of the same-age people in different generations.

3. Results

We calculated the age-standardized reported incidence of hepatitis C by gender among adults aged 30 to 79 in Jilin Province (Fig. 1) and drew age-specific and period-specific age-standardized incidence figures of hepatitis C (Fig. 2) and age-specific and cohort-specific age-standardized incidence figures (Fig. 3). From 2008 to 2017, 62,415 people aged 30 to 79 were diagnosed with hepatitis C.

In this study, suspicious cases were deleted and only clinical diagnosis (27,804 cases) and laboratory confirmation diagnosis (34,611 cases) were included. A total of 54.6% of patients were male (n = 34,097), and 45.4% were female (n = 28,318). Over the past 10 years, the age-standardized reported incidence increased first (34.83 per 100,000 in 2008 and 48.01 per 100,000 in 2011) and then decreased (18.89 per 100,000 in 2017). The overall reported incidence decreased by 46% (Figs. 1 and 2). The reported incidence in men was significantly higher than in women (the average age-standardized incidence of men was 38.27 per 100,000, the average age-standardized incidence of women was 32.01 per 100,000). In 2008 to 2011, the reported incidence

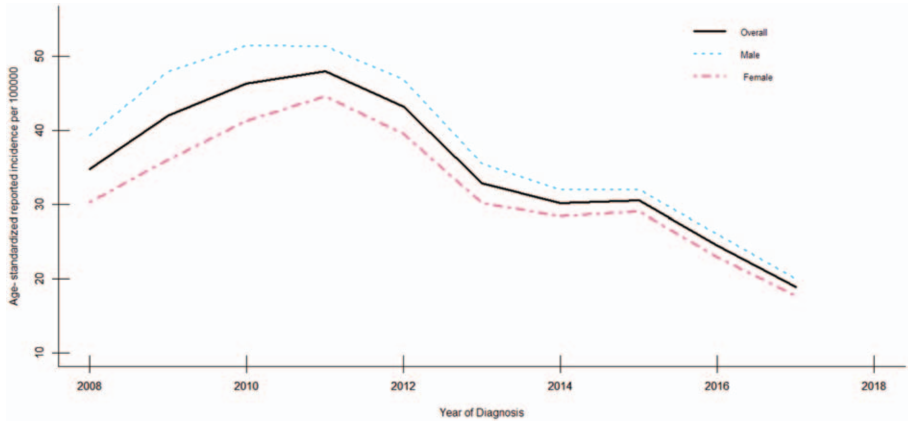

Figure 1. Age-standardized reported incidence of hepatitis C among individuals aged 30 to 79 (/10,000) in Jilin Province, China, in 2008 to 2017.

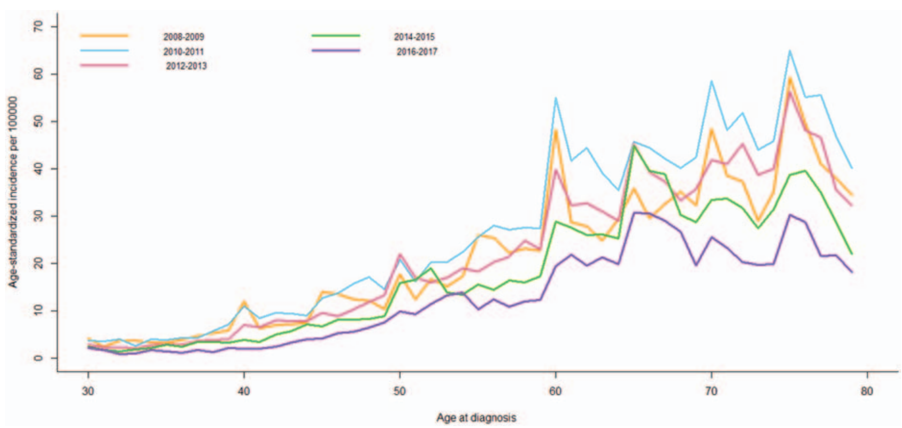

Figure 2. Age-specific and period-specific reported incidence of hepatitis C among individuals aged 30 to 79 in Jilin Province, China, in 2008 to 2017.

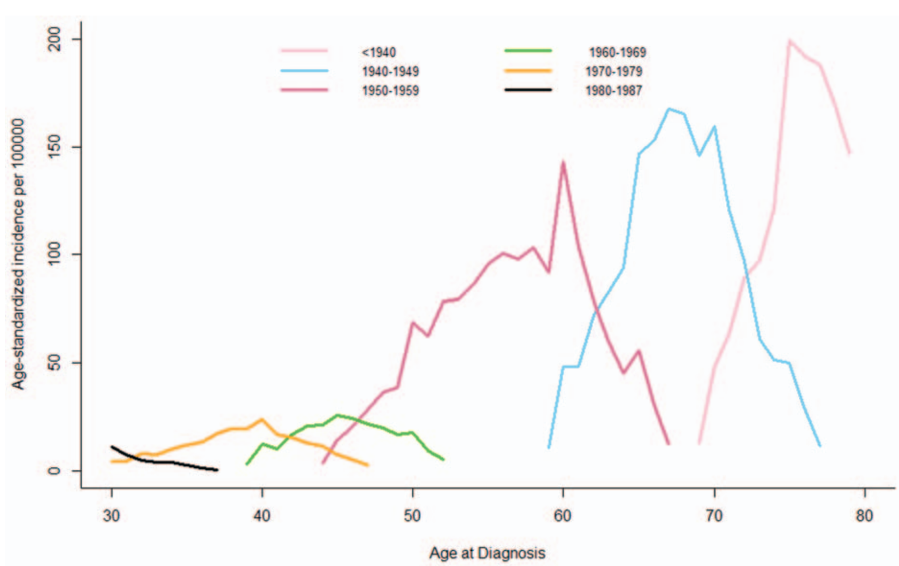

Figure 3. Age-specific and birth-cohort-specific reported incidence of hepatitis C among individuals aged 30 to 79 in Jilin Province, China, in 2008 to 2017.

Table 1

Annual trend changes of reported incidence by sex and age based on joinpoint analysis, 2008 to 2017, Jilin Province.

Sex	Age/year	Calendar period	APC (95%CI)	AAPC (95%CI)
Overall	All	2008–2011	10.4 [−4.1,27.0]	−6.1 [−10.1,−1.8]*
		2011–2017	−13.3 [−17.7,−8.8]*	
	30–44	2008–2011	7.1 [−4.1,19.6]	−10.6 [−14.1,−7.1]*
		2011–2017	−18.4 [−22.6,−13.9]*	
	45–65	2008–2011	10.1 [−4.8,27.4]	−5.9 [−10.1,−1.5]*
		2011–2017	−13.0 [−17.4,−8.3]*	
	66+	2008–2011	12.7 [−4.6,33.2]	−4.3 [−9.1,0.7]
		2011–2017	−11.8 [−16.7,−6.7]*	
Male	All	2008–2011	8.3 [−5.1,23.6]	−7.0 [−10.8,−3.0]*
		2011–2017	−13.8 [−17.9,−9.4]*	
	30–44	2008–2011	5.9 [−3.0,15.7]	−11.1 [−13.8,−8.2]*
		2011–2017	−18.5 [−21.9,−14.9]*	
	45–65	2008–2010	19.6 [−11.3,61.3]	−5.0 [−10.2,0.5]
		2010–2017	−11.1 [−14.6,−7.4]*	
	66+	2008–2011	9.3 [−7.6,29.3]	−6.5 [−11.3,−1.4]*
		2011–2017	−13.5 [−18.5,−8.1]*	
Female	All	2008–2011	13.0 [−3.2,32.0]	−5.0 [−9.5,−0.3]*
		2011–2017	−12.9 [−17.5,−8.0]*	
	30–44	2008–2011	9.4 [−7.7,29.8]	−9.9 [−15.1,−4.3]*
		2011–2017	−18.2 [−24.6,−11.2]*	
	45–65	2008–2011	12.0 [−3.7,30.3]	−5.6 [−10.0,−1.1]*
		2011–2017	−13.4 [−17.9,−8.6]*	
	66+	2008–2011	16.9 [−2.6,40.2]	−2.0 [−7.2,3.6]
		2011–2017	−10.2 [−15.4,−4.8]*	

AAPC = average annual percentage change, APC = annual percentage change.
* $P < .05$.

trends of men and women increased rapidly, and the difference between men and women in the incidence gradually expanded; in 2012 to 2018, the reported incidence trends of men and women decreased, and the difference gradually narrowed (Fig. 1). We found that the reported incidence of hepatitis C increased first and then decreased with increasing age in 10 years (Fig. 2). In the same birth cohort, the reported incidence of hepatitis C also increased first and then decreased with age; in addition to those born in 1980 to 1987, the reported incidence of hepatitis C decreased with age (Fig. 3).

We summarized the results of APC and AAPC in the reported incidence of hepatitis C in Jilin Province (Table 1). Among men, women and the overall population, the reported incidence trend declined in 2008 to 2017, with an average annual decline of 7.0%, 5.0%, and 6.1%, respectively. The trend of 2008 to 2011 was a rapid and significant upward trend and that of 2012 to 2014 was a downward trend. We also observed the situation of each age group, showing a downward trend in all age groups integrally. Among men, women and the overall population aged 30 to 44 years (youth), the reported incidence trend declined the fastest, with an average annual decline of 11.1%, 9.9%, and 10.6%, respectively. Among women and the overall population aged over 66 years (elderly people) and men aged 45 to 65 years (middle-aged people), the reported incidence trend declined the slowest, with an average annual decline of 2.0%, 4.3%, and 5.0%, respectively.

The risk of hepatitis C increased first and then decreased with increasing age. The highest incidence was found in the population aged 55 (Fig. 4A), while it was found in men aged 47 (Fig. 4B) and women aged 76 (Fig. 4C). The periodic effect showed an inverted

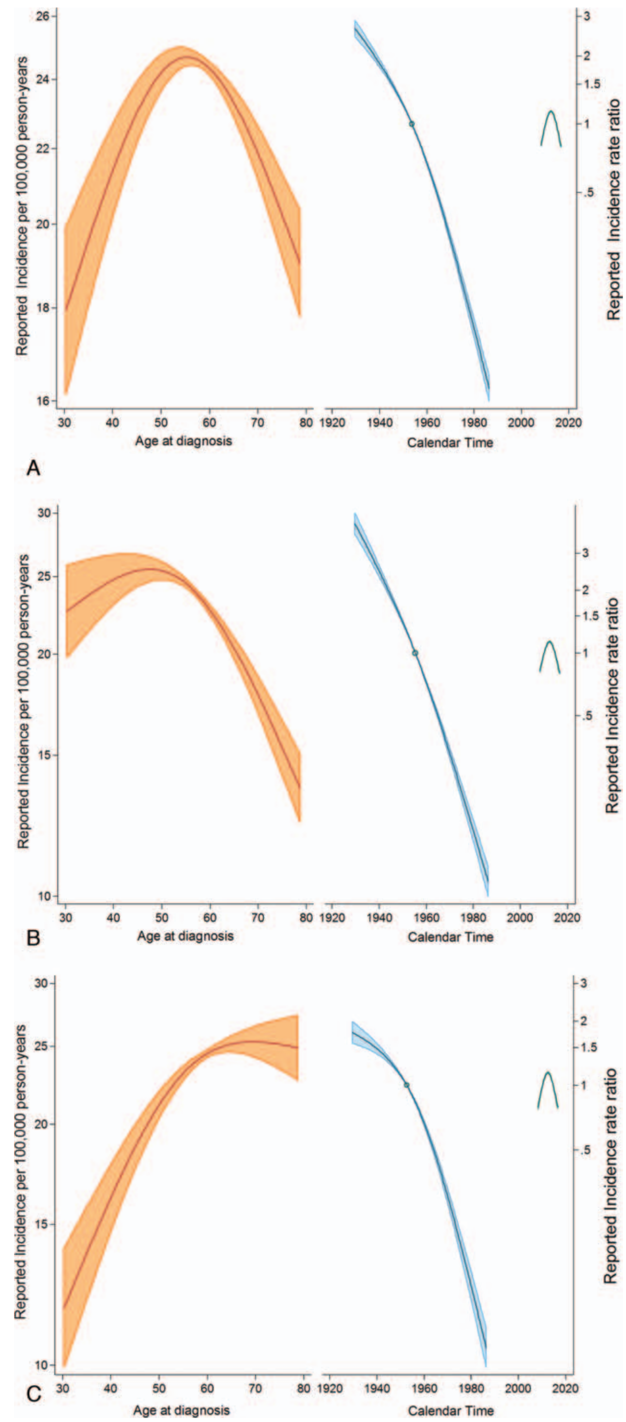

Figure 4. Age-period-cohort model of hepatitis C by sex in Jilin Province, 2008 to 2017. The three regions in the figure represent the estimated effect of age, birth cohort, and period from left to right in the overall population (A), males (B), and females (C); the circle is the reference year (all: 1953, males: 1955, females: 1952); the shaded areas are the 95% CI.

V pattern, and the number of patients diagnosed with hepatitis C increased first and then decreased from 2008 to 2017. We assessed the relative risk of people born in different generations compared with the median birth cohort after adjusting for the period effect and age effect of hepatitis C (Table 2). Among the total population, the risk of hepatitis C increased by 158% in the

Table 2

Birth-cohort effects on hepatitis C based on age-period-cohort analysis.

	All	Male	Female
1930	2.58 (2.38,2.79)	4.03 (3.59,4.52)	1.75 (1.56,1.96)
1940	1.83 (1.76,1.90)	2.41 (2.27,2.56)	1.47 (1.39,1.55)
1950	1.19 (1.18,1.20)	1.37 (1.35,1.40)	1.10 (1.09,1.11)
1960	0.66 (0.65,0.67)	0.69 (0.68, 0.70)	0.64 (0.62,0.66)
1970	0.29 (0.28,0.31)	0.32 (0.30,0.34)	0.30 (0.27,0.32)
1980	0.12 (0.11,0.13)	0.14 (0.12,0.16)	0.11 (0.10,0.13)

Birth-cohort effects are expressed in terms of the reported incidence rate ratios (95% CI) compared with the median birth year (all: 1953, males: 1955, females: 1952), $P < .01$ for all comparisons of birth years.

same age group born in 1930, 83% in the same age group born in 1940 and 19% in the same age group born in 1950, compared with the median reference year (1953). The risk of hepatitis C was reduced by 34% for people of the same age born in 1960, 71% for people of the same age born in 1970 and 88% for people of the same age born in 1980, compared with the median reference year (1953). Similarly, the risk of hepatitis C was reduced in both male and female populations after adjusting for period and age effects. This trend was more obvious and steeper in men. Men born in 1930 were four times more likely to develop hepatitis C than those born in 1955.

4. Discussion

In conclusion, in this study, the standardized reported incidence of hepatitis C showed a downward trend as a whole, and the reported incidence in men declined more rapidly than that in women. We found that the reported incidence showed an upward trend before 2011 and then showed a downward trend. It may be mainly affected by the Yanbian Prefecture hepatitis C prevention and control project carried out by the Center for Disease Control and Prevention in Jilin Province in 2010. Since 2010, the widespread use of a nucleic acid test in blood transfusion screening for hepatitis C virus (HCV) in China has led to a rapid decline in the reported incidence of transfusion-related hepatitis C.[14] But, China has low rates of HCV testing, including men who have sex with men. A nationwide cross-sectional online survey in China found 59% had never HCV tested.[15] The results of the age effect suggested that age may be one of the important factors influencing hepatitis C and that the reported incidence increased first and then decreased with increasing age. The overall reported incidence was the highest in those 50 to 60 years old. Men <55 years old and women over 60 years old had the highest incidence, which may indicate that men under 55 and women over 60 years old are at high risk. Recent evidence suggests that 70.1% of the infected people are in the age group of 45 to 65 years old in the United States.[16] Previous studies have reported that the incidence trend of hepatitis C among people aged over 55 in China shows a significant growth trend.[17] The results of our study are similar to these findings. The mild clinical symptoms of acute infection are mostly unrecognized and will progress to persistent infection. Patients often have complications of end-stage liver disease before they are diagnosed with hepatitis C. The stage may last for 20 to 30 years.[18] It contributed to the reported incidence associated with HCV. As a result, patients diagnosed with hepatitis C are often middle-aged or elderly individuals. Men have a higher prevalence of alcohol abuse than women in China.[19] HCV infection have a higher prevalence of alcohol abuse compared with the general population. Alcohol and hepatitis virus have synergistic effects in the development of liver disease, which leaded to faster rates of progression towards symptomatic cirrhosis.[20] Because of gender and alcohol abuse, men are younger than women when diagnosed, or testing for hepatitis C is more prevalent among men.

The period effect increased first and then decreased, and the risk reached a peak in the middle of the study. Other studies of the age-period-cohort analysis in Henan Province of China have pointed out that the period effect of hepatitis C infection rates showed a continuous upward trend over time.[21] In fact, with the development of the Chinese economy, health care and living standards, the reported incidence of hepatitis C should show a downward trend. In particular, in recent years, the application of direct-acting antiviral agents has been safe and effective.[22] We can predict that the reported incidence of hepatitis C will decrease significantly in the long term. In 2016, the World Health Organization put forward a global strategy for eliminating HCV by 2030. China has also launched a health plan for eliminating HCV,[23] including improving blood safety, such as HCV screening for blood donors and blood products,[14] Infection control measures such as methadone maintenance therapy, which may be used in antiviral treatment for people who inject drugs,[24,25] as well as the implementation of expanded testing, will lead to a long-term decline in reported incidence. We know that the risk factors of hepatitis C include high-risk sexual behavior, injecting drugs, blood transfusion, medical environmental pollution and poor behavior habits.[26–28] Therefore, the above factors may lead to an increase in reported incidence with time.

The cohort effect results showed a downward trend. This change may be brought about by social development and health care services, including reducing the risk of exposure to hepatitis C virus in health care institutions and in high-risk populations, as well as managing patients infected with hepatitis C virus. The risk of blood transfusion caused by infectious diseases has been significantly reduced after effective blood product donor screening and improved pathogen detection in China.[14] For people who inject drugs, methadone maintenance therapy and needle syringe programs implemented by the Chinese government can prevent the spread of hepatitis C virus.[24,29] Studies have shown that the treatment of patients with hepatitis C infection can reduce the transmission of hepatitis C.[30] In the 2015 edition of the "Guide to the Prevention and Treatment of Hepatitis C" in China, treatment projects with DAAs have also been included. People over 55 years old are more likely to be diagnosed with HCV infection due to related complications. So we cannot ignore the low rates of detection and diagnosis in the young birth cohort.

Although we found that the reported incidence of hepatitis C in Jilin Province has a certain downward trend, the cohort effect also showed a downward trend. However, China is still facing a serious burden of hepatitis C at this stage, and the disease burden is likely to increase in the next few years. China is in a period of rapid aging. In 2013, the number of elderly people over 60 years old exceeded 200 million.[31] In Jilin Province, the proportion of elderly people aged 65 and over reached 10.91% at the end of 2015. According to the data of the sixth nationwide population census in 2010, Jilin Province is one of the 16 net outflow areas with a net outflow of ~916,000. The working-age population has shrunk, and the elderly population has expanded. A continuous increase in the level of aging will lead to an increase in the number of people at high risk of hepatitis C and an increase in the burden of disease in the future. Moreover, individuals infected with HCV are more likely to develop human immunodeficiency virus or hepatitis B virus infection, which will accelerate the process of liver fibrosis and make treatment more complicated.[32] The genetic diversity of the hepatitis C virus has led to many challenges in the development of a hepatitis C vaccine, which has not yet been marketed as an effective method to prevent hepatitis C.[33] In China, especially in rural areas, the popularity rate of hepatitis C knowledge is very low, which will greatly increase the risk of transmission to others.[34] In addition, some studies have reported that the incidence of hepatitis C caused by the prevalence of opioids in recent years is also on the rise,[8] and cosmetic and dental treatments and even imprisonment are emerging risk factors for hepatitis C,[35–37] which are still reasons for the increase in the burden of hepatitis C disease. Therefore, although the overall reported incidence of hepatitis C in Jilin Province has declined, we should continue to pay attention to the prevention and control of hepatitis C and completely eliminate it. Therefore, there is still a long way to go to prevent and control hepatitis C. We can start with early screening, especially for people over 50 years of age, to achieve early detection, early diagnosis and early treatment.

There are some limitations in this study. First, the time span of the data is relatively short, and we still need to collect data with a longer time span to further explore the impact of different periods of medical policy and the improvements in the screening, diagnosis and treatment technology on the reported incidence of hepatitis C. Second, we used surveillance data, we did not determine the main causes of hepatitis C, we could not study the trend of changes in the etiology of hepatitis C, nor did we have detailed data on the incidence of hepatitis C in urban and rural areas, and we could not compare the urban and rural differences in the incidence of hepatitis C. Reported incidence could not represent a real incidence, a decrease in reported incidence may be a decrease in testing activity. Finally, because of the absence of data on mortality, we currently cannot estimate the recent changes in mortality to fully study the epidemic characteristics of hepatitis C.

5. Conclusion

Although the reported incidence of hepatitis C in Jilin Province has generally declined, there is a problem of population aging, and the majority of residents lack knowledge about hepatitis C prevention and control. At present, there is no preventive hepatitis C vaccine. Our work on the prevention and control of hepatitis C should focus on avoiding high-risk behaviors, timely detection and standardized treatment.

Author contributions

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Visualization: Shan Jiang.
Writing – original draft: Qinglong Zhao, Shan Jiang.
Writing – review & editing: Qinglong Zhao, Shan Jiang, Meina Li, Laishun Yao, Meng Li, Bo Li.

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