

Trends in mortality of liver disease due to hepatitis B in China from 1990 to 2019: findings from the Global Burden of Disease Study

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Abstract

Background: Hepatitis B is a viral infection that attacks the liver and can cause both potentially life-threatening acute and chronic liver disease. China has the world's largest burden of hepatitis B and is considered to be a major contributor toward the goal of World Health Organization (WHO) of eliminating hepatitis B virus (HBV) as a global health threat by 2030. This study aimed to analyze data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) to determine the trends in mortality of liver disease due to hepatitis B in China between 1990 and 2019 and the gap with the WHO's goal.

Methods: Annual deaths and age-standardized mortality rates (ASMRs) of liver disease due to hepatitis B in China between 1990 and 2019 were collected from GBD 2019. We calculated the percentage changes in deaths and estimated annual percentage changes (EAPCs) of ASMRs of liver disease due to hepatitis B.

Results: In China, deaths of total liver disease due to hepatitis B decreased by 29.13% from 229 thousand in 2016 to 162 thousand in 2019, and ASMR decreased by an average of 4.92% (95% confidence interval [CI]: 4.45–5.39%) per year in this period. For the spectrum of liver disease due to hepatitis B, deaths decreased by 74.83%, 34.71%, and 23.34% for acute hepatitis, cirrhosis and other chronic liver diseases, and liver cancer from 1990 to 2019, respectively, and ASMRs of acute hepatitis (EAPC = -7.63; 95% CI: -8.25, -7.00), cirrhosis and other chronic liver diseases (EAPC = -4.15; 95% CI: -4.66, -3.65), and liver cancer (EAPC = -5.17; 95% CI: -6.00, -4.33) decreased between 1990 and 2019. The proportions of older adults aged ≥ 70 years among all deaths of the spectrum of liver disease due to hepatitis B increased from 1990 to 2019. Deaths of liver cancer due to hepatitis B increased by 7.05% from 2015 to 2019.

Conclusions: Although a favorable trend in the mortality of liver disease due to hepatitis B was observed between 1990 and 2019, China still faces challenges in achieving the WHO's goal of eliminating HBV as a public threat by 2030. Therefore, efforts to increase the coverage of diagnosis and treatment of liver disease due to hepatitis B, especially of liver cancer due to hepatitis B, are warranted in China.

Keywords: Hepatitis B; Acute hepatitis B; Chronic liver disease; Liver cirrhosis; Liver neoplasms; Global Burden of Disease; Global Health; China

Introduction

Hepatitis B virus (HBV), the etiological agent of acute and chronic HBV infection in humans, leads to a potentially life-threatening liver infection.^[1,2] There is a wide spectrum of liver diseases caused by HBV infection, ranging from acute hepatitis (including fulminant hepatic failure) to chronic hepatitis, cirrhosis, and liver cancer (hepatocellular carcinoma).^[3] Acute hepatitis B is usually an acute self-limited infection and is marked by acute inflammation and hepatocellular necrosis, which can lead to the development of acute liver failure and death.^[4,5] Among chronically infected persons, many of them have mild liver disease with little or no long-term morbidity or mortality, and a subset of them develop advanced liver

diseases such as cirrhosis and hepatocellular carcinoma, which cause high morbidity and mortality.^[3] HBV infection is a major global health problem, causing high mortality and disease burden worldwide.^[6] Globally, it was estimated that there were 154 million new cases of acute hepatitis B infection in 2017 and 296 million people living with chronic hepatitis B infection in 2019.^[7,8] The World Health Organization (WHO) estimated that 820,000 deaths were caused by hepatitis B in 2019 worldwide, mostly by cirrhosis and primary liver cancer.^[8] In 2016, WHO's Global Strategy for Viral Hepatitis endorsed the goal of eliminating viral hepatitis, including hepatitis B, as a public health threat by 2030.^[9] The targets of this elimination goal were defined as achieving a 90% reduction in new chronic infections and a

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65% reduction in mortality by 2030 compared with the 2015 baseline.^[10]

China is the country with the world's largest burden of HBV infection, with an estimated 90 million persons chronically infected with HBV in 2017.^[11] In addition, deaths due to HBV-related liver diseases in China accounted for >30% of the global mortality from HBV.^[12] Thus, China is considered as a major contributor to the WHO's goal of eliminating HBV as a public health threat by 2030. In the past 3 decades, China has made remarkable progress in the prevention and control of HBV and the diagnosis and treatment of hepatitis B.^[11-14] In 2017, entecavir and tenofovir, the two WHO-recommended medicines for the treatment of hepatitis B, were included in the updated national list of reimbursable medicines in China.^[11] The decision signifies critical progress toward universal coverage for hepatitis B treatment in China. In addition, in 2018, when tenofovir came off patents in China, the costs of medicines were expected to drop, which should further increase treatment access.^[11] Based on the remarkable progress in HBV prevention and control and critical progress in hepatitis B treatment, China has changed from a highly endemic area into an intermediate endemic area for HBV infection.^[12-14] However, the trend in mortality of liver disease due to hepatitis B in the past 3 decades is unknown. In addition, because of the priority to combat chronic hepatitis B over the past decades, progress in understanding acute hepatitis B has been limited.^[15] It is necessary to emphasize the trends in mortality of liver disease due to hepatitis B, including acute hepatitis B, cirrhosis and other chronic liver diseases due to hepatitis B, and liver cancer due to hepatitis B, to combat HBV infection in China. Therefore, we retrieved detailed data on the mortality of total liver diseases due to hepatitis B, acute hepatitis B, cirrhosis and other chronic liver diseases due to hepatitis B, and liver cancer due to hepatitis B in China from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 to determine the trends in mortality of liver disease due to hepatitis B in the past 3 decades and to provide a more comprehensive perspective for targeted interventions and health policies for HBV prevention and control in China.

Methods

Data source

The GBD was developed and maintained by the Institute for Health Metrics and Evaluation at the University of Washington, which aims to provide rigorous and comparable measurements of important health problems across the globe.^[16] The GBD systematically collects mortality data and applies a standard methodological approach to generate estimates for mortality by sex, age group, and disease for countries around the world. International Classification of Diseases codes were used to deaths assigned for nonspecific, implausible, or intermediate causes of death in the GBD.^[17] The GBD provides age-standardized mortality rate (ASMR) data by sex and disease for countries by applying age-specific rates for each location, sex, and year to a GBD World Standard

Population to adjust for potential confounding of age structure.^[18] More details about the data collection and modeling of GBD can be found elsewhere.^[7,19] GBD data on all-cause and cause-specific death in China were primarily derived from surveillance systems, including the Disease Surveillance Point System and the Maternal and Child Surveillance System, as well as from surveys, the China Cancer Registry, and the Chinese Center for Disease Control and Prevention cause-of-death reporting system.^[20,21] This study used data of annual deaths and ASMRs of liver disease due to hepatitis B, including total liver disease due to hepatitis B, acute hepatitis B, cirrhosis and other chronic liver diseases due to hepatitis B, and liver cancer due to hepatitis B in China between 1990 and 2019 from the GBD 2019.^[16] Specific methods of GBD study 2019 estimation process for the mortality of liver disease due to hepatitis B have been described elsewhere.^[18,22]

Statistical analysis

We calculated the percentage changes in deaths of liver disease due to hepatitis B, including total liver disease due to hepatitis B, acute hepatitis B, cirrhosis and other chronic liver diseases due to hepatitis B, and liver cancer due to hepatitis B, from 1990 to 2019. The percentage changes in deaths of liver disease due to hepatitis B from 1990 to 2019 were calculated by the equation: Percentage changes = $\frac{\text{Deaths in 2019} - \text{Deaths in 1990}}{\text{Deaths in 1990}} \times 100\%$. In addition, we calculated the estimated annual percentage changes (EAPCs) in ASMRs of total liver disease due to hepatitis B and the spectrum of liver disease due to hepatitis B to quantify their trends between 1990 and 2019. The EAPC is a summary and widely used measure of the ASMR trend over a specified time interval. A regression line was fitted to the natural logarithm of the ASMR, that is, $y = \alpha + \beta x + \varepsilon$, where $y = \ln(\text{ASMR})$ and $x = \text{calendar year}$. The EAPC in ASMRs was calculated as $100 \times (e^{\beta} - 1)$, and its 95% confidence interval (CI) was calculated to reflect the temporal trend in ASMRs. The trend in ASMR was reflected in the EAPC value and its 95% CI: ASMR is in an upward trend when the EAPC and the lower boundary of the 95% CI are positive; conversely, ASMR is in a downward trend when EAPC and the upper boundary of the 95% CI are negative. Finally, we divided age into four specific age groups: <35, 35–49, 50–69, and ≥ 70 years in this study. Then, the age-specific proportions of deaths of total liver disease due to hepatitis B and the spectrum of liver disease due to hepatitis B between 1990 and 2019 were calculated. All analyses were conducted with SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and OriginPro 2015 (OriginLab, Northampton, MA, USA). A two-tailed P value <0.05 was considered statistically significant.

Results

Trends in mortality of liver diseases due to hepatitis B in China

In 2019, total liver diseases due to hepatitis B resulted in 162 thousand deaths in China, including 3 thousand deaths of acute hepatitis B (1.78%), 42 thousand deaths of

Table 1: The deaths and ASMRs of liver diseases due to hepatitis B in 1990 and 2019 and their change trends from 1990 to 2019.

Characteristics	1990		2019		1990–2019	
	Deaths, $N \times 10^5$ (95% UI)	ASMR per 100,000, N (95% UI)	Deaths, $N \times 10^5$ (95% UI)	ASMR per 100,000, N (95% UI)	Percentage change in deaths (%)	EAPC in ASMR N (95% CI)
Total	2.29 (1.94, 2.71)	24.67 (21.05, 29.04)	1.62 (1.33, 1.95)	8.07 (6.66, 9.69)	-29.13	-4.92 (-5.39, -4.45)
Sex						
Male	1.76 (1.44, 2.13)	37.82 (31.00, 45.29)	1.33 (1.04, 1.65)	13.75 (10.92, 16.91)	-24.44	-4.63 (-5.14, -4.10)
Female	0.53 (0.42, 0.65)	11.83 (9.58, 14.42)	0.29 (0.23, 0.37)	2.86 (2.26, 3.56)	-44.72	-5.62 (-5.91, -5.32)
Spectrum of liver disease due to hepatitis B						
Acute hepatitis B	0.11 (0.08, 0.17)	1.18 (0.82, 1.77)	0.03 (0.02, 0.04)	0.16 (0.13, 0.19)	-74.83	-7.63 (-8.25, -7.00)
Cirrhosis and other chronic liver diseases	0.65 (0.55, 0.75)	7.27 (6.16, 8.43)	0.42 (0.34, 0.51)	2.16 (1.73, 2.61)	-34.71	-4.15 (-4.66, -3.65)
Liver cancer	1.53 (1.26, 1.84)	16.22 (13.47, 19.53)	1.17 (0.95, 1.43)	5.76 (4.68, 7.02)	-23.34	-5.17 (-6.00, -4.33)

ASMR: Age-standardized mortality rate; CI: Confidence interval; EAPC: Estimated annual percentage change; UI: uncertainty interval.

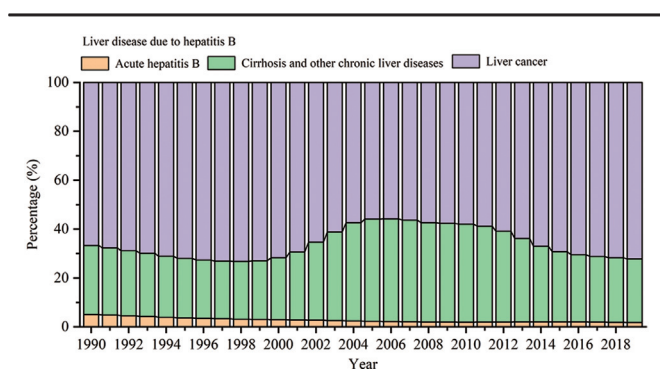


Figure 1: Contribution of acute hepatitis B, cirrhosis and other chronic diseases due to hepatitis B, and liver cancer due to hepatitis B to absolute deaths of total liver diseases due to hepatitis B in China from 1990 to 2019.

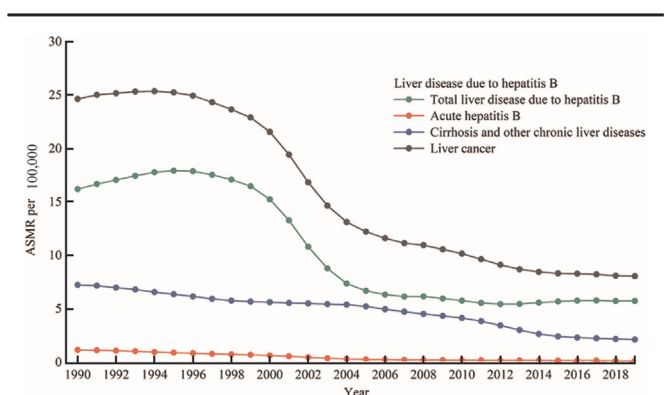


Figure 2: The ASMRs of total liver diseases due to hepatitis B, acute hepatitis B, cirrhosis and other chronic liver diseases due to hepatitis B, and liver cancer due to hepatitis B in China from 1990 to 2019. ASMR: Age-standardized mortality rate.

cirrhosis and other chronic liver diseases due to hepatitis B (26.04%), and 117 thousand deaths of liver cancer due to hepatitis B (72.18%) [Table 1 and Figure 1]. Between 1990 and 2019, >95% of the deaths of total liver diseases due to hepatitis B were ascribed to cirrhosis and other chronic liver diseases, and liver cancer due to hepatitis B [Figure 1]. The proportions of deaths due to acute hepatitis B among all deaths due to hepatitis B were low and decreased in this period [Figure 1]. From 1990 to 2019, the number of total liver diseases due to hepatitis B in China decreased by 29.13% from 229 thousand to 162 thousand [Table 1]. The numbers of deaths of total liver diseases due to hepatitis B decreased by 24.44% for males (from 176 thousand in 1990 to 133 thousand in 2019) and 44.72% for females (from 53 thousand in 1990 to 29 thousand in 2019) in this period [Table 1]. For the spectrum of liver disease due to hepatitis B, the numbers of deaths decreased by 74.83% for acute hepatitis B, 34.71% for cirrhosis and other chronic liver diseases, and 23.34% for liver cancer from 1990 to 2019 [Table 1].

In 2019, the ASMR of total liver diseases due to hepatitis B was 8.07 (95% UI: 6.66, 9.69) per 100,000 and was higher among males (13.75 per 100,000) than among females (2.86 per 100,000) [Table 1]. For the spectrum of liver disease due to hepatitis B, the ASMRs were 0.16, 2.16, and 5.76 per 100,000 for acute hepatitis B, cirrhosis

and other chronic liver diseases, and liver cancer in 2019 [Table 1]. From 1990 to 2019, the ASMR of total liver diseases due to hepatitis B decreased by an average of 4.92% (95% CI: 4.45%, 5.39%) per year [Table 1 and Figure 2]. The ASMRs were deemed to be in a decreasing trend for acute hepatitis B (EAPC = -7.63; 95% CI: -8.25, -7.00), cirrhosis and other chronic liver diseases due to hepatitis B (EAPC = -4.15; 95% CI: -4.66, -3.65), and liver cancer due to hepatitis B (EAPC = -5.17; 95% CI: -6.00, -4.33) in this period [Table 1 and Figure 2].

Age-specific deaths of liver diseases due to hepatitis B in China

For total liver diseases due to hepatitis B, the reduced number of deaths was due to the gradual reduction in the number of deaths in the population aged <70 years, especially in the population aged 35 to 69 years between 1990 and 2019 [Figure 3A]. However, the number of deaths of total liver diseases due to hepatitis B increased among older adults aged ≥70 years between 1990 and 2019 [Figure 3A]. The reduced number of deaths of acute hepatitis B was due to the gradual reduction in all age groups between 1990 and 2019, especially in the population aged <35 years [Figure 3B]. Similar to total liver diseases due to hepatitis B, the numbers of deaths of cirrhosis and other chronic liver diseases and liver cancer

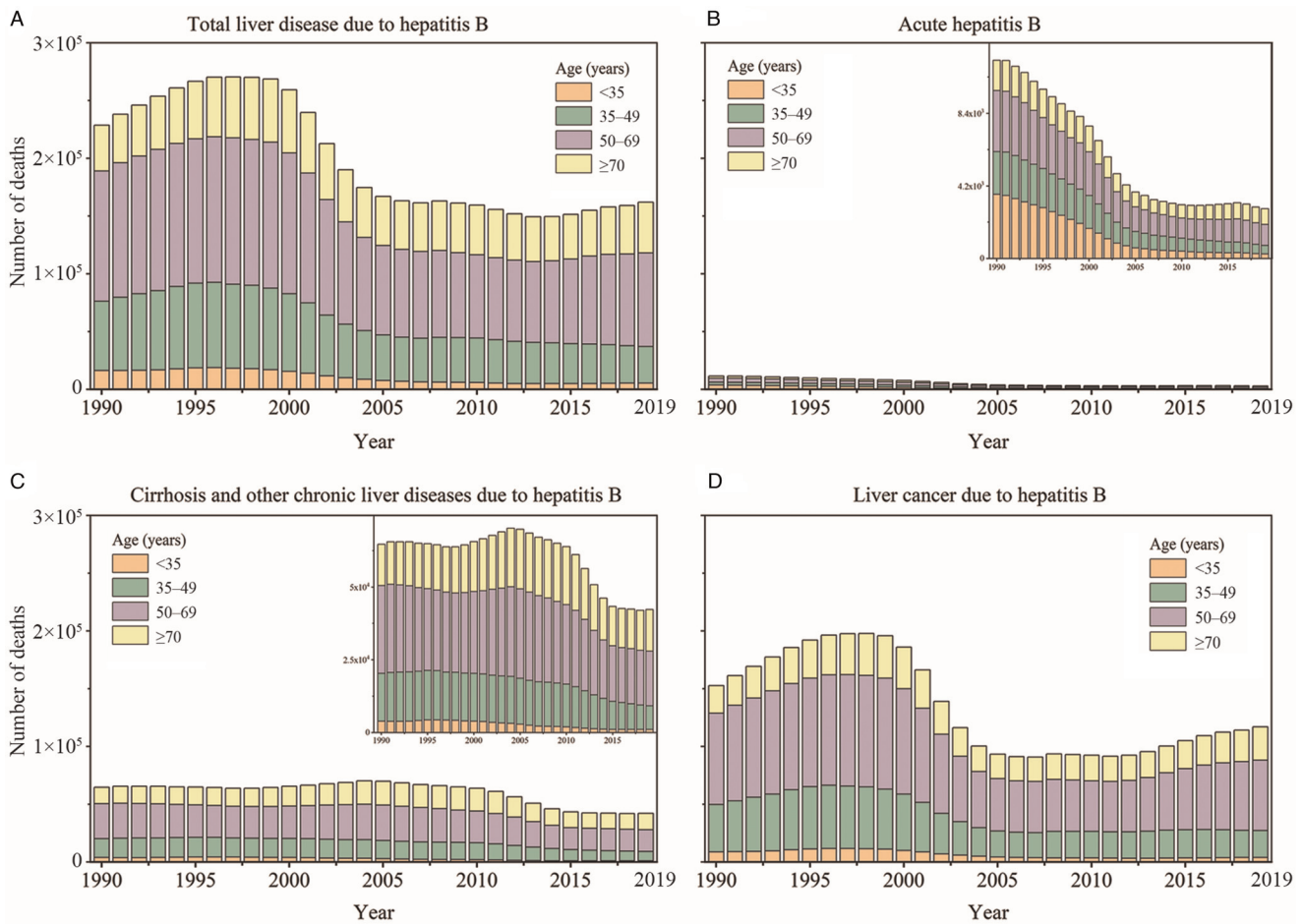


Figure 3: The age distribution of deaths of total and spectrum of liver diseases due to hepatitis B in China between 1990 and 2019. (A) The age distribution of deaths of total liver diseases due to hepatitis B in China between 1990 and 2019; (B) The age distribution of deaths of acute hepatitis B in China between 1990 and 2019, with an enlarged figure shown at the top right; (C) The age distribution of deaths of cirrhosis and other chronic liver diseases due to hepatitis B in China between 1990 and 2019, with an enlarged figure shown at the top right; (D) The age distribution of deaths of liver cancer due to hepatitis B in China between 1990 and 2019.

due to hepatitis B decreased among the population aged <70 years but increased among older adults aged ≥70 years between 1990 and 2019 [Figure 3C,D]. From 2015 to 2019, the numbers of deaths slightly decreased for acute hepatitis B and cirrhosis and other chronic liver diseases; however, the number of deaths of liver cancer due to hepatitis B increased by 7.05% from 109 thousand to 117 thousand in this period, leading to an increased number of deaths of total liver disease due to hepatitis B [Figure 3B–D].

For the deaths of total liver diseases due to hepatitis B, the proportion of the population aged <50 years decreased from 1990 to 2019, while the proportion of older adults ≥50 years increased in this period [Figure 4A]. Similar changes were also observed in deaths of acute hepatitis B [Figure 4B]. For the deaths of cirrhosis and other chronic liver diseases and liver cancer due to hepatitis B, the proportion of the population aged ≥70 years increased from 1990 to 2019 [Figure 4C,D].

Discussion

Our study is the first to provide the trends in the mortality of liver disease due to hepatitis B, including total liver diseases, acute hepatitis, cirrhosis and other chronic liver

diseases, and liver cancer in China in the past 3 decades based on the latest GBD 2019. In this study, we found that 98.22% of the deaths of liver disease due to hepatitis in China were attributed to cirrhosis and other chronic liver diseases due to hepatitis B (26.04%) and liver cancer due to hepatitis B (72.18%) in 2019. From 1990 to 2019, the numbers of deaths of acute hepatitis B, cirrhosis and other chronic liver diseases, and liver cancer due to hepatitis B separately decreased by 74.83%, 34.71%, and 23.34% in China, resulting in a 29.13% reduction in total liver diseases due to hepatitis B. Meanwhile, the ASMRs of liver disease due to hepatitis B in China decreased by an average of 4.92%, 7.63%, 4.15%, and 5.17% per year for total liver diseases, acute hepatitis B, cirrhosis and other chronic liver diseases, and liver cancer between 1990 and 2019, respectively. Although the deaths of both cirrhosis and other chronic liver diseases and liver cancer due to hepatitis B decreased from 1990 to 2019 from an overall perspective, the numbers increased in older adults aged ≥70 years. The number of deaths of liver cancer due to hepatitis B increased by 7.05% from 2015 to 2019, and the numbers of deaths of acute hepatitis B cirrhosis and other chronic liver diseases due to hepatitis B slightly decreased in this period.

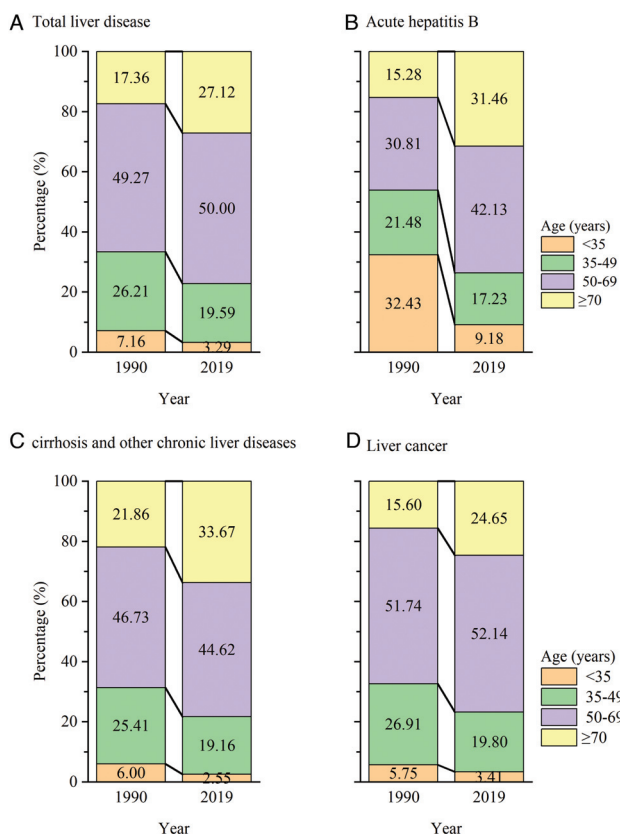


Figure 4: Contribution to absolute deaths of total and spectrum of liver diseases due to hepatitis B by age group in China in 1990 and 2019. (A) Contribution to absolute deaths of total liver diseases due to hepatitis B by age group in China in 1990 and 2019; (B) Contribution to absolute deaths of acute hepatitis B by age group in China in 1990 and 2019; (C) Contribution to absolute deaths of cirrhosis and other chronic liver diseases due to hepatitis B by age group in China in 1990 and 2019; (D) Contribution to absolute deaths of liver cancer due to hepatitis B by age group in China in 1990 and 2019.

This study found that the main cause of death from liver disease due to hepatitis B was liver cancer due to hepatitis B, followed by cirrhosis and other chronic liver diseases due to hepatitis B and acute hepatitis B in 2019. This is due to the disease progression and clinical outcomes with different mortality risks after HBV infection. The occurrence of symptoms and the progression of liver diseases during acute HBV infection depend on the hosts' age at infection.^[5,6] Acute HBV infection in infants and children is mostly asymptomatic, whereas approximately 30% of adults have icteric hepatitis and 70% have subclinical or anicteric hepatitis.^[6] Less than 1% of adults with acute HBV infection can develop fulminant hepatic failure, which has a mortality of approximately 80% without liver transplantation.^[6] Approximately 95% of neonates, 20% to 30% of children aged 1 to 5 years and <5% of adults with acute HBV infection develop chronic infection.^[5,6] A total of 25% to 40% of chronic HBV infection progresses to liver fibrosis and cirrhosis and eventually progresses to decompensated liver disease and/or hepatocellular carcinoma, which cause high morbidity and mortality.^[2,4,23] Thus, efforts to achieve a 65% reduction in mortality of the global elimination of viral hepatitis by 2030 need to focus on chronic HBV infection, especially on liver cancer due to hepatitis B.

Both the deaths and ASMRs of liver disease due to hepatitis B, including acute hepatitis B, cirrhosis and other chronic liver diseases due to hepatitis B, and liver cancer due to hepatitis B decreased in China between 1990 and 2019. The decreased mortality of liver disease due to hepatitis B in China was possibly ascribed to improvements in hepatitis B vaccination coverage, testing and diagnosis of HBV infection, and antiviral treatment of patients with chronic hepatitis B.^[12] Since 1992, China has enacted a universal hepatitis B vaccination program for newborns and infants.^[24] The coverage of the timely birth-dose of hepatitis B vaccine increased from 22.2% in 1992 to 95.6% in 2015,^[16,25] and the coverage of three doses of hepatitis B vaccine for infants increased from 30.0% in 1992 to 99.4% in 2019 in China.^[16,26] The Chinese government requires medical institutions to screen for hepatitis B in patients who are undergoing surgery, hospitalization, hemodialysis, or invasive diagnosis and treatment and in all pregnant women during antenatal care, which increases the coverage of HBV infection testing.^[12,27] As far as the treatment of HBV infection is concerned, there is no specific treatment for acute hepatitis B, and antiviral treatment in patients with chronic hepatitis B is typically a lifelong commitment. Available treatment options for chronic HBV infection include nucleoside analogs, interferon- α , and pegylated interferon- α .^[28] Entecavir, tenofovir, or pegylated interferon- α is recommended for treatment-naïve chronic HBV patients.^[28] According to data from the China Registry of Hepatitis B, 88.7% of patients treated for chronic hepatitis B were receiving nucleoside analog therapy in 2016.^[29] The WHO recommended the treatment of hepatitis B with entecavir and tenofovir, which have been included in the updated national list of reimbursable medicines in China since 2017.^[11] Until 2017, all of the antiviral drugs recommended by the Chinese guidelines (interferon- α , pegylated interferon- α , and five nucleoside analogs) were included in the national basic medical insurance reimbursement list as partial out-of-pocket expenses, contributing to the improvement of treatment coverage.^[28,30]

In this study, we found that the number of deaths of older adults aged ≥ 70 years due to liver disease due to hepatitis B increased between 1990 and 2019, which is possibly due to the low hepatitis B vaccine coverage among them.^[16,24] In addition, the numbers of acute hepatitis B and cirrhosis and other chronic liver diseases due to hepatitis B decreased slightly from 2015 to 2019, and the numbers of deaths of total liver disease due to hepatitis B increased due to the increased number of deaths of liver cancer due to hepatitis B in this period, indicating large gaps toward the elimination of HBV infection by 2030 in China. Thus, efforts to increase the coverage of diagnosis and treatment of liver disease due to hepatitis B, especially of liver cancer due to hepatitis B, are warranted in China. In addition, it is also necessary for the surveillance of chronic hepatitis B, which can be beneficial for reducing mortality of liver disease due to hepatitis B.

This current study comprehensively assessed the trends in mortality of total liver diseases due to hepatitis B, acute hepatitis B, cirrhosis and other chronic liver diseases due

to hepatitis B, and liver cancer due to hepatitis B between 1990 and 2019 using data from GBD estimates, which fill a gap where actual data on disease burden are sparse or unavailable. However, several limitations should be noted. First, the availability of data and the quality of available data limited the accuracy and robustness of the estimates of the mortality of liver disease due to hepatitis B in the modeling,^[18] which might have caused bias when national surveillance and population-based studies were lacking. Second, EAPC in ASMRs and relative change in the number of deaths of liver disease due to hepatitis B were used to assess its long-term trends from 1990 to 2019, which might mask the recent short-term trends that reflected the effectiveness of the recent prevention interventions of liver disease due to hepatitis B. Third, this study lacks estimates for the different provinces in China.

In summary, the number of deaths and ASMR of liver diseases due to hepatitis B in China gradually decreased from 1990 to 2019. The numbers of liver disease due to hepatitis B increased in older adults aged ≥ 70 years from 1990 to 2019, and the numbers of deaths of liver cancer due to hepatitis B increased from 2015 to 2019. China still faces challenges in achieving the WHO's goal of eliminating HBV as a public threat by 2030. Therefore, efforts to increase the coverage of diagnosis and treatment of liver disease due to hepatitis B, especially of liver cancer due to hepatitis B, are warranted in China. Future studies on identifying risk factors for liver disease-related deaths due to hepatitis B are warranted.

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Conflicts of interest

None.

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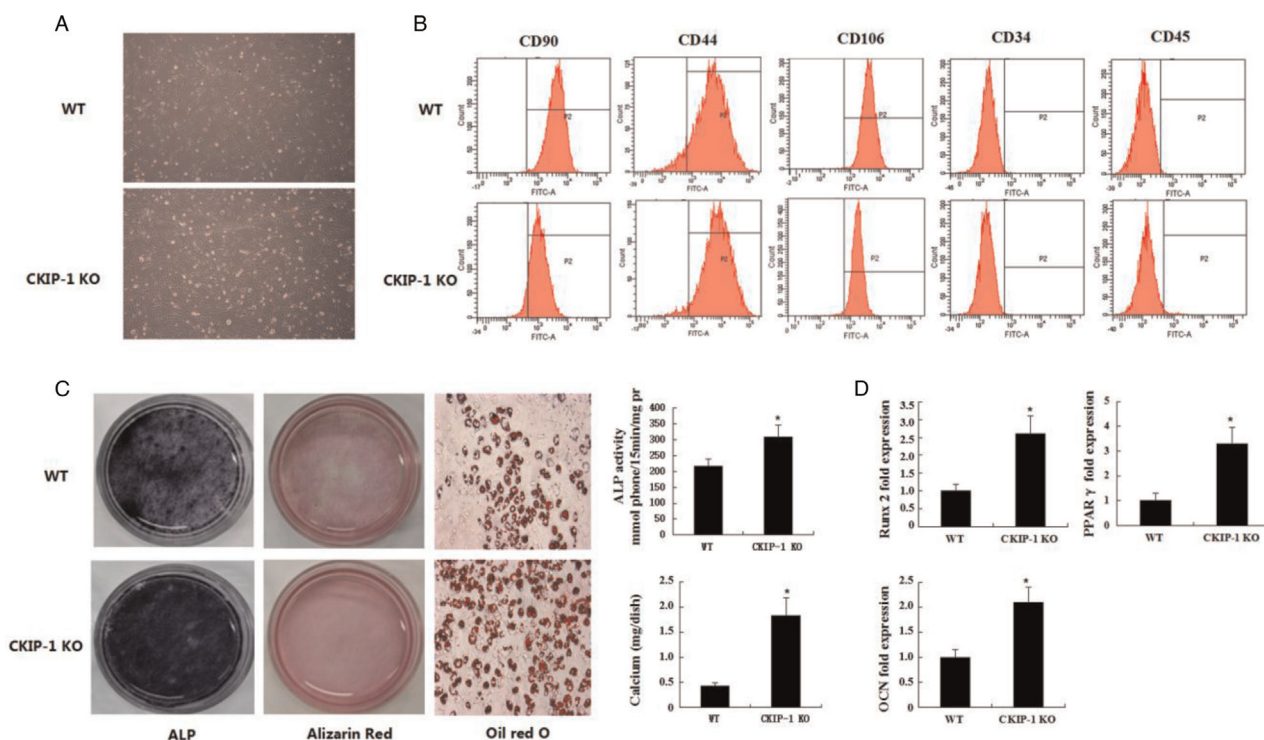
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Corrigendum

Corrigendum: Inflammation-mediated age-dependent effects of casein kinase 2-interacting protein-1 on osteogenesis in mesenchymal stem cells

Following the original article’s publication,^[1] the authors informed us of the following errors:^[1] The Figure 1 was submitted incorrectly, while correct Figure 1 should be submitted as following:

The authors apologize for any inconvenience caused.



Reference

1. Tian XG, Gong FF, Li X, Meng FH, Zhou Z, Zhang HZ. Inflammation-mediated age-dependent effects of casein kinase 2 interacting protein-1 on osteogenesis in mesenchymal stem cells. *Chin Med J* 2020;133:1935–1942. doi: 10.1097/CM9.0000000000000951.