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Original Article

Mortality Burden of Liver Cancer in China: An Observational Study From 2008 to 2020

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Abstract

Background and Aims: China accounts for nearly half of liver cancer deaths globally. A better understanding of the current liver cancer mortality will be helpful to establishing priorities for intervention and to decreasing the disease burden of liver cancer. The study aimed to explore and predict the mortality burden of liver cancer in China. ***Methods:*** Data were extracted from the Disease Surveillance Point system of the Chinese Center for Disease Control and Prevention from 2008 to 2020. Crude and age-standardized liver cancer mortality rates were reported by sex, urban or rural residence, and region. Trends in liver cancer mortality rates from 2008 to 2020 were estimated as average annual percentage change (AAPC). The changing trend of live cancer mortality in the future is also predicted. ***Results:*** In 2020, the crude mortality of liver cancer was 25.57/100,000, and males and people lived in rural areas had higher age-standardized liver cancer mortality rates than females and people lived in people in urban areas. Crude mortality and age-standardized mortality rates in southwest provinces (Guangxi, Sichuan, Tibet) and in a northeast province (Heilongjiang) were higher than that in other provinces, and age-specific mortality rates increased with age. From 2008 to 2020, liver cancer mortality rates decreased, but people under 50 years of age had a higher AAPC than those over 50 years of age, possibly because of the adoption of hepatitis B virus vaccination in newborns and children. Furthermore, the mortality of liver cancer in 2021–2030 is predicted to have a downward trend. ***Conclusions:*** Liver cancer mortality rates declined in China from 2008 to 2020. Future interventions to control liver cancer mortality need to focus on people of male sex, older age, and living in rural areas or less developed provinces.

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Introduction

Liver cancer is the sixth most frequently diagnosed cancer and the third leading cancer-related cause of death worldwide. Globally, approximately 830,180 people with liver cancer died in 2020,[1] with 75–85% of those having hepatocellular carcinoma (HCC) and 10–15% having intrahepatic cholangiocarcinoma, and other rare types. Liver cancer was the second leading cause of cancer death in China in 2020, followed by lung cancer.[2] Even after efforts to prevent and control liver cancer, the number of deaths in China accounted for nearly half of liver cancer deaths worldwide (49.89% males and 40.78% females).[1–4] Liver cancer remains a severe public health problem in China, and liver cancer mortality has a significant impact on the global burden of liver cancer. Understanding the current and changing profiles of liver cancer mortality in China in recent decades will be helpful in establishing priorities for intervention and reducing the global disease burden of liver cancer.

Prior studies used part of Chinese mortality surveillance system data to depict the trends of all cancer mortality, showed that the mortality of liver cancer decreased in recent years,[5] and one study used global disease burden data reported the estimated disease burden of liver cancer due to specific etiologies in China from 1990 to 2019.[6] However, to

Keywords: Liver cancer; Mortality; Burden; Trend; China; Prediction.

Abbreviations: AAPC, average annual percentage change; ASMRC, age-standardized mortality rate adjusted by the Chinese standard population; ASMRW, age-standardized mortality rate adjusted by the world standard population; CDC, Chinese Center for Disease Control and Prevention; CI, confidence interval; DAAs, direct-acting antiviral drugs; DSPs, Disease Surveillance Point System; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; ICD, International Classification of Diseases; NAFLD, nonalcoholic fatty liver disease; SDI, sociodemographic index.

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our knowledge, no studies have reported the mortality rates for the entire country and provinces over time with the sociodemographic index (SDI) for liver cancer based on national surveillance data. In the current study, we used detailed information from the Disease Surveillance Points system (DSPs) of the Chinese Center for Disease Control and Prevention (CDC) to report the mortality rates of liver cancer by region, residential location, province, as well as by age-group and sex, trend of mortality rate by sex and residence location, and region.

Methods

Data source

Mortality data of patients with liver cancer from 2008 to 2020 were collected from the DSPs. The DSPs was introduced by the Ministry of Health of China in 1980, and gradually adjusted its coverage and representativeness over the following decades.[7] In 2004, the number of surveillance points of DSPs expanded to 161, including 64 urban and 97 rural locations, across 31 provinces in mainland China. The DSPs covered 73 million residents, which is about 6% of the Chinese population.[8] In 2008, all the mortality data was reported through an online system. In 2013, the surveillance points were expanded to 605 using a multistage stratified cluster random sampling method, covering 323.8 million residents, which is about 24% of the total Chinese population. Deaths at the surveillance points were collected and coded using the International Classification of Disease, 10th Revision (ICD-10) by trained staff in hospitals or the local CDC. Duplicate records of death were eliminated by county or provincial CDC staff. In addition, underreporting surveys were conducted every 3 years to determine the amount of underreporting of mortality rates, and crude mortality rates were adjusted by dividing 1 minus corresponding underreporting rate.[9,10] The reliability of the data and national representativeness have been demonstrated by previous studies.[7,11–13] In the DSPs, causes of death were coded by ICD-10 codes. The ICD-10 codes for liver cancer were C22–C22.9.

Demographic data extracted from the DSPs included age, sex, residential location (urban and rural areas), and region (Eastern, Central, and Western China). Regions were classified according to the National Statistics Bureau. Eastern China included Beijing, Tianjin, Hebei, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan. Central China included Heilongjiang, Jilin, Shanxi, Henan, Hubei, Anhui, Jiangxi, and Hunan. Other provinces were grouped as Western China. The study was approved by the Ethics Committee of National Center for Chronic and Noncommunicable Disease Control and Prevention of the CDC (No. 202219-1). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki revised in 2013.

Statistical analysis

The numbers of deaths and mortality rates of liver cancer were extracted from the DSPs database. Mortality rates were expressed as the number of deaths caused by liver cancer per 100,000 people (1/100,000), and were adjusted by the corresponding underreporting rate to determine the accurate crude mortality rates. Age-standardized mortality rates of liver cancer were calculated using the 2010 census population of China (ASMRC) and Segi's population (ASMRW), respectively.

We reported crude mortality rate, ASMRC, and ASMRW by sex, region (Eastern China, Central China, and Western China) and residential location (urban and rural areas), as well as age group (<30 years of age, 30–85-year intervals, and >85 years of age). We estimated the average annual percentage change (AAPC) of liver cancer mortality rate from 2008 to 2020 with 95% confidence intervals (CIs) using Joinpoint Regression software (version 4.9.0.0, National Cancer Institute, Bethesda, MA, USA).[14] Statistical analysis was conducted in the Joinpoint Regression Program, all testing was two-sided with statistical significance set at $\alpha=0.05$.

Results

Mortality of liver cancer in 2020

In 2020, 86,692 deaths were reported in the DSPs in China. The overall crude mortality of liver cancer was 25.57 per 100,000 people and was 36.63 per 100,000 in males, 14.05 per 100,000 for females, 28.59 per 100,000 for rural areas, and 21.37 per 100,000 for urban areas. Males had higher age-standardized mortality rates than females (ASMRC: 30.15/10.01 per 100,000 people, ASMRW: 23.04/7.54 per 100,000 people). Compared with urban areas, rural areas had higher age-standardized mortality rates (ASMRC: 16.66/22.29 per 100,000 people, ASMRW: 12.69/16.98 per 100,000 people). After stratified by regions (Eastern, Central and Western China), the trends remained the same (Table 1).

Supplementary Table 1 showed the crude mortality rates and ASMRC of liver cancer from 31 provinces in 2020. The highest crude mortality rates of liver cancer were in provinces from southwest (Guangxi, Sichuan) and northeast China (Heilongjiang) China. These mortality rates were higher than 46.38 per 100,000 people. After adjusted by age structure, Guangxi province had the highest ASMRC (42.18–67.59 per 100,000 people). Meanwhile, Tibet, Sichuan and Chongqing in Western China, Heilongjiang, Jilin, Henan and Jiangxi in the Central China, and Fujian and Guangdong in Eastern China also had higher ASMRCs than other provinces (32.21–42.17 per 100,000 people). The lowest ASMRC was in Xinjiang, a province from northwest China (12.30–15.07 per 100,000 people) (Supplementary Table 1). After stratified by sex, the geographical distribution characteristics of the crude mortality rates and ASMRC of liver cancer in males and females were similar with the whole population (Supplementary Tables 2–3).

Age-specific mortality rate of liver cancer stratified by sex, residential location, and region in 2020

The age-specific mortality rates of liver cancer increased with age, but in males from rural areas, the age-specific mortality rate in over 85 years old group was lower than in 80–84 years old group (Supplementary Table 4, Supplementary Fig. S1B); the same situation was seen in males from urban areas in Eastern China and females in Western China (Supplementary Table 4). After stratified by sex, the age-specific mortality rate in males was higher than that in females for each age group. After stratified by residential locations (urban and rural areas) and regions (Eastern, Central and Western China), males still had higher age-specific mortality rates than females (Fig. 1, Supplementary Figs. 1 and 2, Supplementary Table 4).

Trends in mortality of liver cancer from 2008 to 2020

The overall ASMRC of liver cancer in China had a downward trend from 2008 to 2020, and the decline remained after stratified by sex, residential location, and region (Fig. 2A, B). From 2008 to 2020, there was no difference in AAPC neither between different sexes [AAPC in females: −4.1 (95% CI: −4.8 to −3.5) vs. AAPC in males −4.4 (95% CI: −5 to −3.7)] nor between different residential locations [AAPC in urban areas: −3.3 (95% CI: −4.2 to −2.5) vs. AAPC in rural ar-

Table 1. Mortality rates of liver cancer by sex, region, and location in 2020 in China

Region	Location	Sex	Crude rate ($1/10^5$)	ASMRC ($1/10^5$)	ASMRW ($1/10^5$)
All	All	Both	25.57	19.92	15.19
		Male	36.63	30.15	23.04
		Female	14.05	10.01	7.54
	Urban	Both	21.37	16.66	12.69
		Male	30.35	25.07	19.21
		Female	11.95	8.5	6.35
	Rural	Both	28.59	22.29	16.98
		Male	41.17	33.9	25.86
		Female	15.55	11.07	8.37
Eastern China	All	Both	22.53	16.97	13
		Male	32.56	26.1	20.05
		Female	12.04	8.16	6.16
	Urban	Both	18.54	14.38	11.03
		Male	26.29	21.85	16.86
		Female	10.28	7.13	5.35
	Rural	Both	26.18	19.28	14.74
		Male	38.39	29.98	22.94
		Female	13.61	9.04	6.84
Central China	All	Both	29.09	22.56	17.18
		Male	40.92	33.5	25.53
		Female	16.9	12.08	9.14
	Urban	Both	24.57	18.85	14.30
		Male	34.91	28.2	21.45
		Female	13.94	9.87	7.43
	Rural	Both	31.23	24.37	18.56
		Male	43.76	36.1	27.51
		Female	18.31	13.14	9.96
Western China	All	Both	26.86	22.34	16.91
		Male	38.91	33.76	25.68
		Female	14.26	11.04	8.23
	Urban	Both	24.18	19.33	14.61
		Male	34.57	28.79	21.97
		Female	13.45	10.1	7.42
	Rural	Both	28.84	24.67	18.7
		Male	42.08	37.6	28.55
		Female	14.87	11.78	8.85

ASMRC, age-standardized mortality rate adjusted by the Chinese standard population; ASMRW, age-standardized mortality rate adjusted by the world standard population.

eas: −4.6 (95% CI: −5.4 to −3.8)] (Fig. 2A, Supplementary Tables 5 and 6). When stratified by region, there were also no differences in the AAPC in Eastern, Central, and Western China (Fig. 2B, Supplementary Table 7).

AAPC of age-specific mortality rate of liver cancer from 2008 to 2020

From 2008 to 2020, age-specific mortality rates of liver cancer decreased in both males and females (AAPC<0), except for males 50–59 years of age and females 75–79 and >85 years of age (Fig. 3). The AAPC of age-specific mortality rate was higher in people younger than 50 years of age than it was in people older than 50 years of age. This difference remained after stratified by residential locations and regions (Fig. 3).

After stratified by regions, in Eastern China, the age-specific mortality rate of liver cancer decreased in almost

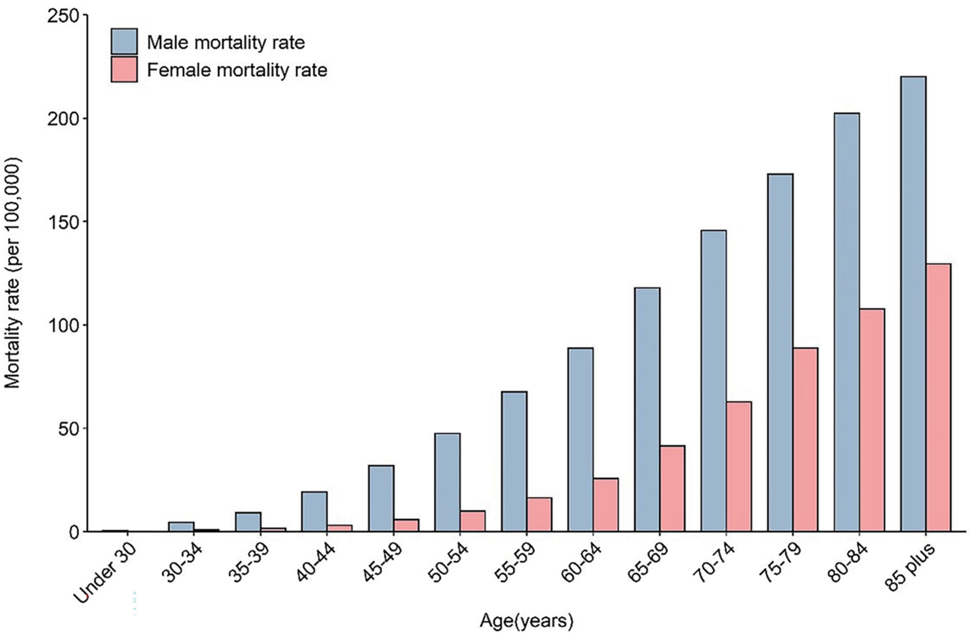

Fig. 1. Mortality rates of liver cancer in 2020 by age and sex.

every group except females over 85 years of age. In Central China, the age-specific mortality rate decreased in individuals 35–49, 60–74, and 80–84 years of age. However, in Western China, the age-specific mortality rate of liver cancer hadn't decreased in many age groups, and only decreased in those who were 40–44, 60–74, and 25–29 years of age (Fig. 3).

Time trends of age-standardized mortality rate of liver cancer with SDI

From 2008 to 2020, the ASMRC of liver cancer increased with an SDI of 0.4–0.6, but decreased with an SDI greater than 0.6 (Fig. 4). When taking a closer look at the data in Figure 4 stratified by province, the ASMRC of liver cancer decreased or held steady as SDI increased in most provinces, but in provinces in Western China, Tibet, Guangxi province, and Chongqing province the ASMRC increased with SDI before their SDI exceed 0.6. The high-income Guangdong province in Eastern China had the largest decrease in liver cancer ASMRC with SDI between 2008–2020, as shown in Figure 4.

Prediction of mortality of liver cancer from 2021 to 2030

The age-standardized mortality rate (ASMRC) of liver cancer is predicted to have a downward trend in 2021–2030 (16.86–12.33/100,000) (Fig. 5). After dividing the whole population into males and females, the trend is consistent with the overall population (males 25.42–18.83/100,000 and females 8.25–5.60/100,000) (Figs. 6 and 7).

Discussion

We conducted a comprehensive evaluation of liver cancer mortality in China in 2020 and analyzed the mortality trend from 2008 to 2020. After adjusting for age structure, males had higher mortality rates than females in 2020. Mortality rates were higher in rural areas and provinces in southwest and northeast China than in urban areas and provinces in other regions. The age-specific mortality rates of liver cancer increased with age. The mortality rate of liver cancer had a descending trend in 2008–2020, with a larger decrease in females, younger people, and people from Eastern China. Moreover, the expected liver cancer ASMRC had an upward trend with SDIs of <0.6 and a downward trend when the SDI was >0.6. These findings will be helpful to target the priority intervention group of people to decrease the mortality of liver cancer.

There are many risk factors associated with liver cancer, including hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol intake, dietary aflatoxin, nonalcoholic fatty liver disease, cirrhosis, smoking, low vegetable consumption, drug use, and radiation exposure.[15–21] In China, chronic HBV and HCV infections are still the major contributors for liver cancer.[22,23] Our study showed that the mortality rate of liver cancer decreased significantly between 2008 and 2020. This result might be attributed to administration of the hepatitis B vaccine and the use of direct-acting antiviral agents (DAAs) for HCV. Since 1992, China has made great efforts to combat HBV, mandating HBV vaccination for newborns.[24,25] Subsequently, an HBV vaccination catch-up program for children 8–15 years of age for the whole country began in 2009.[16] All these efforts have led to a significant decrease in the positivity rate of hepatitis B surface antigen (HBsAg), resulting in a decrease in the incidence and mortality of HBV-related liver cancer. In our study, from 2008 to 2020, the AAPC of liver cancer ASMRC in individuals younger than 50 years of age was greater than that of people older than 50 years of age. This might be due to HBV vaccination in newborns in China since 1992 and the catch-up HBV vaccination program in children since 2009.[16,24,25] The HBV vaccine immunization rate was incomplete in old people when they were young, which may have led to the higher liver cancer mortality.[26] No effective vaccine to prevent HCV infection is currently available, but the introduction of DAAs has substantially reduced the burden of HCV in China. According to one clinical trial in

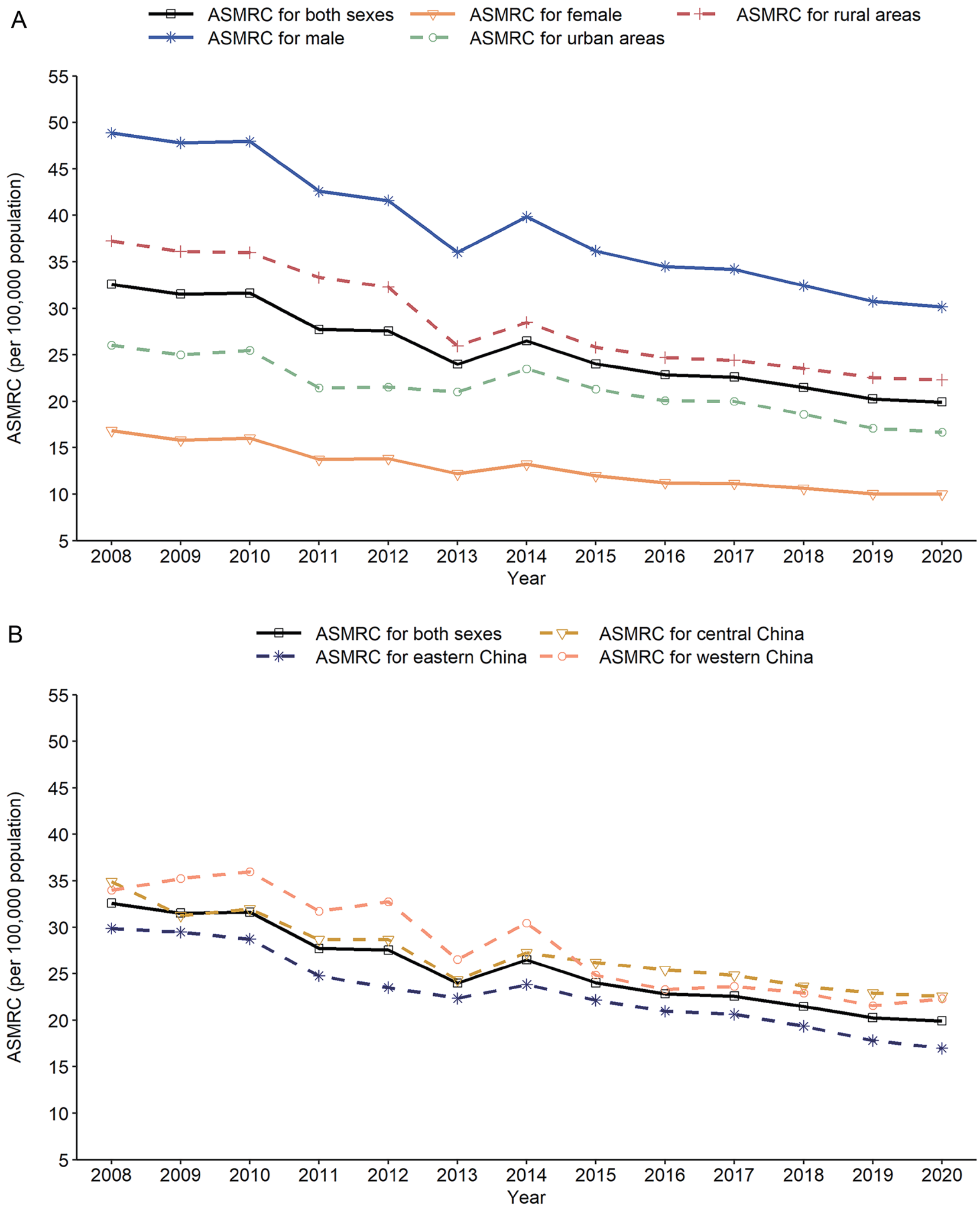

Fig. 2. Trends in ASMRC of liver cancer in 2008–2020 by the sex, residence, and region in China. (A) By sex and residence. (B) By region. ASMRC, the age-standardized mortality rate of China.

China, DAA treatment was safe and well-tolerated,[27] and the investigators recommended rapid expansion of DAAs to all HCV-infected patients. The prevalence of chronic HCV is expected to decrease to 7.97 million in 2050.[28] However, we did not observe a decrease in liver mortality in people 25–29 years in urban areas, <34 years of age in Central China, and 30–39 years of age in Western China. That might be attributed to alcohol consumption in adolescents, which is an emerging problem in China and may lead to an increasing incidence of alcohol-associated liver cancer in young people.[16,29]

Our study found that the deaths of liver cancer in males was significantly higher than that in females. Females had a larger AAPC of liver cancer mortality from 2008 to 2020. This might be explained by the following evidence. Firstly, multiple serological surveys in China found that males had

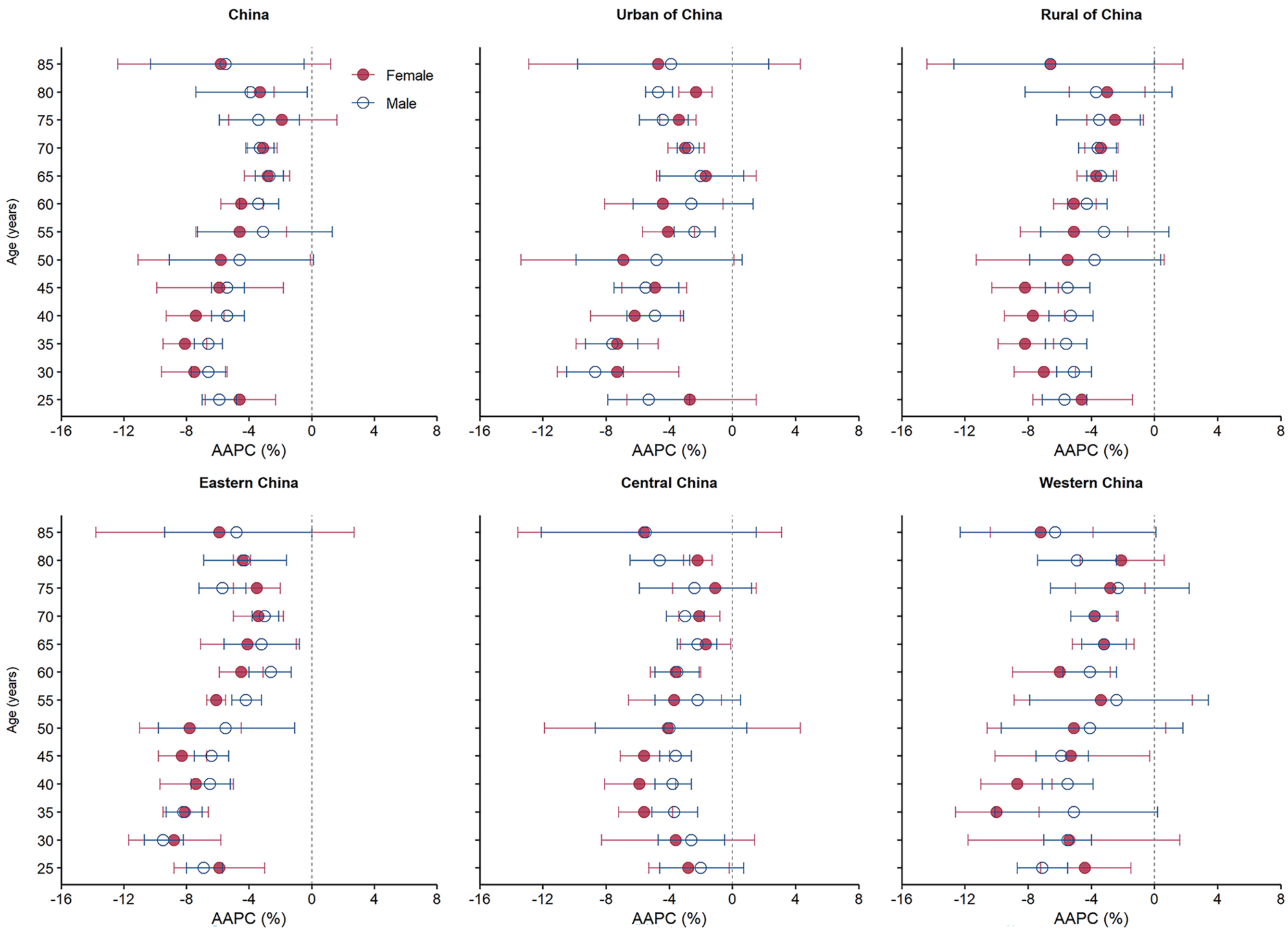

Fig. 3. Average annual percentage change (AAPC) of liver cancer by the sex, region and residence in 2008–2020 in China.

higher HBsAg-positive rates than females, and the HBsAg positive rate of males to females was increasing gradually.[30,31] Secondly, males were more likely to be infected with HBV and HCV and have increased iron stores, which might be associated with the specific sex.[32] Finally, in China, alcohol abuse in adolescents is still a common and an emerging problem, and compared with female, males consume more alcohol.[29,33,34] Thirdly, tobacco smoking is an attributable cause of liver cancer mortality, national smoking surveys in China reported that the prevalence of smoking was higher in males than that in females.[23]

Both crude mortality and age-standardized mortality rates were higher in rural than that in urban areas. The disparity of liver cancer mortality between urban and rural areas was consistent with other reports.[5,32,35] Compared with rural residents, individuals residing in urban areas may pay more attention to their health.[36] Unequal medical resources exist between these two locations, for instance in the availability of antiviral therapy for HBV and HCV, and treatment of liver cirrhosis and liver cancer.[35] In addition, the main risk factors, such as HBV and HCV infection, aflatoxin, and sanitary contamination, are more prevalent in rural areas.

In this study, we found that the mortality rate for liver disease was higher in some provinces in Central and Western China (Heilongjiang, Guangxi, Sichuan, and Tibet) than that in Eastern China. The results are consistent with those of previous studies.[32,37] The HBsAg positivity rate was higher in Heilongjiang, Guangxi, and Sichuan than that in other provinces. In addition to chronic HBV infection, aflatoxin contamination in central and western China, and special dietary habits (e.g., spicy food) and humid climate in southwest China may be associated with death of liver cancer.[38–40] The HBsAg positivity rate in Tibet was the highest in China, but liver cancer mortality was low, possibly because most liver cancer patients died at home and mortality was not accurately monitored.[41]

The mortality of liver cancer decreased with SDI when SDI exceeded 0.6. This most likely resulted from improvement of sanitary and medical conditions, as well as people's health awareness. It is worth noting that liver cancer mortality had an upward trend in Tibet and Guangxi with SDI before it exceeded 0.6. With less developed geographic regions, most people die at home without medical diagnosis owing to inconvenient transportation and low health service availability. With the increase in SDI, more death liver cancer deaths were diagnosed, which can explain the upward trend of reported liver cancer mortality.[39,41,42]

Conclusions

We conducted a long-term data analysis of liver cancer mortality in China from 2008 to 2020 using data from the

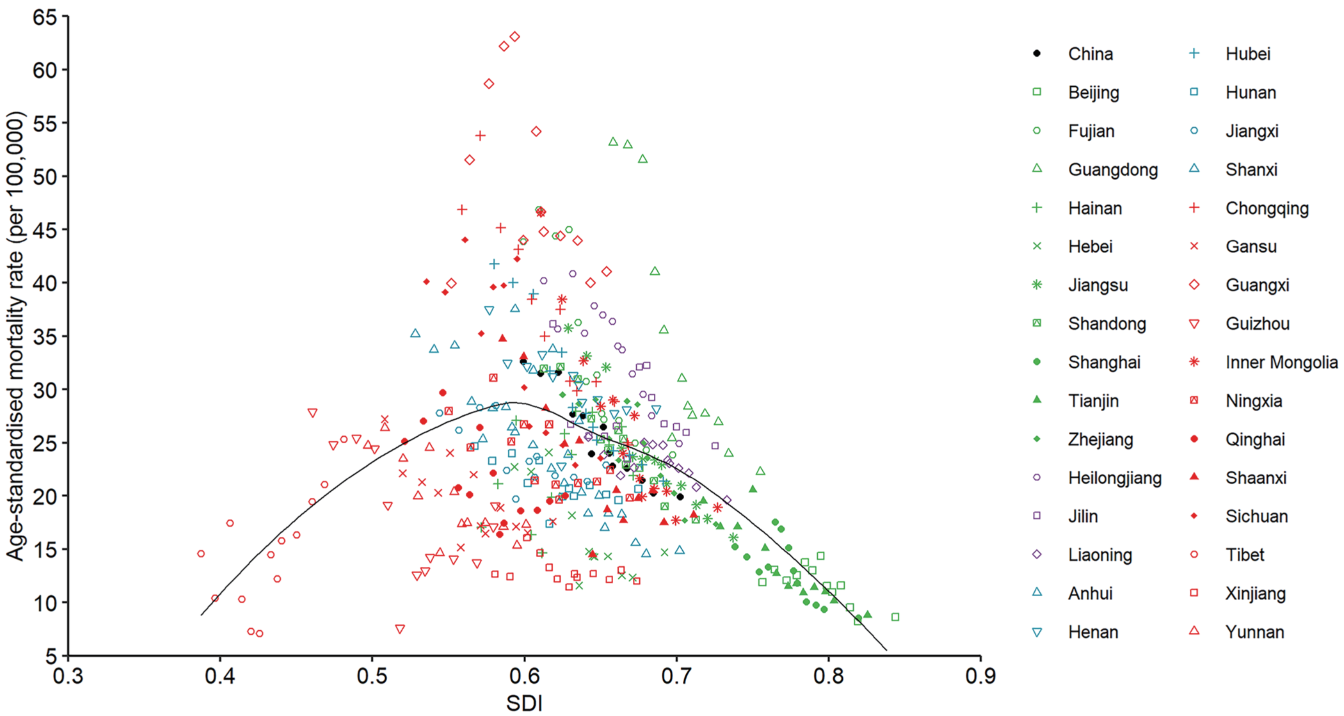

Fig. 4. Age-standardized mortality rates per 100,000 for liver cancer by SDI in 2008–2020 in China. SDI, sociodemographic index.

CDC-DSPs. There was an overall decreasing trend of liver cancer mortality in China in the last decade except for people 50–59 years of age and females 75–79 and >85 years of age. A higher liver cancer mortality burden was observed in males, older people, and people living in rural areas or less developed provinces. In the future, interventions to control liver cancer mortality need to focus on these groups.

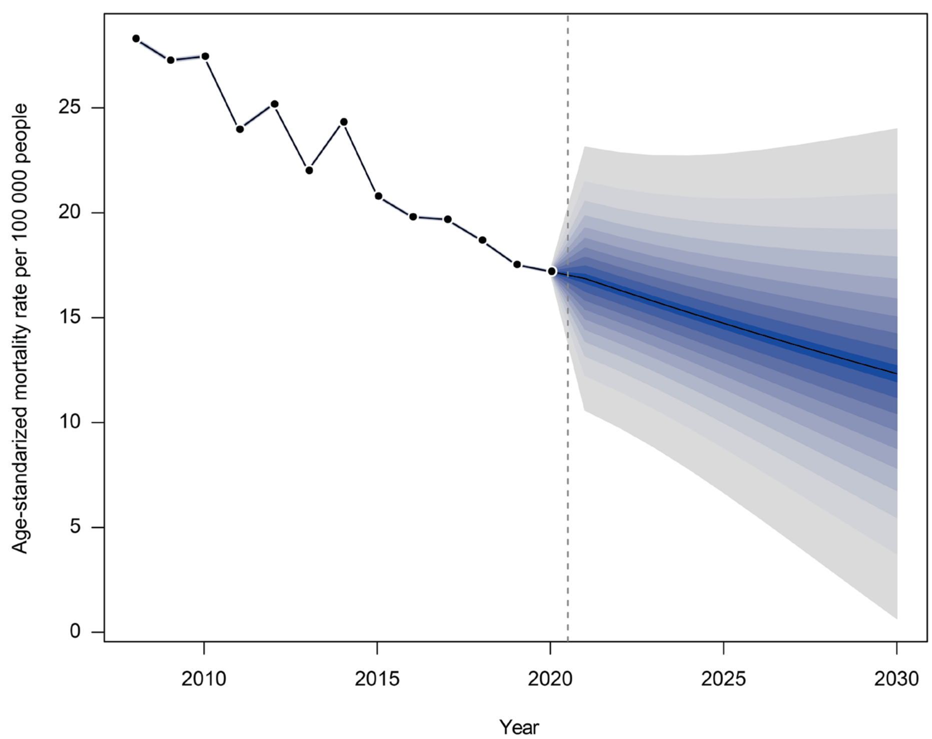

Fig. 5. Prediction of the ASMRC for liver cancer in all population in 2021–2030 in China. ASMRC, the age-standardized mortality rate of China.

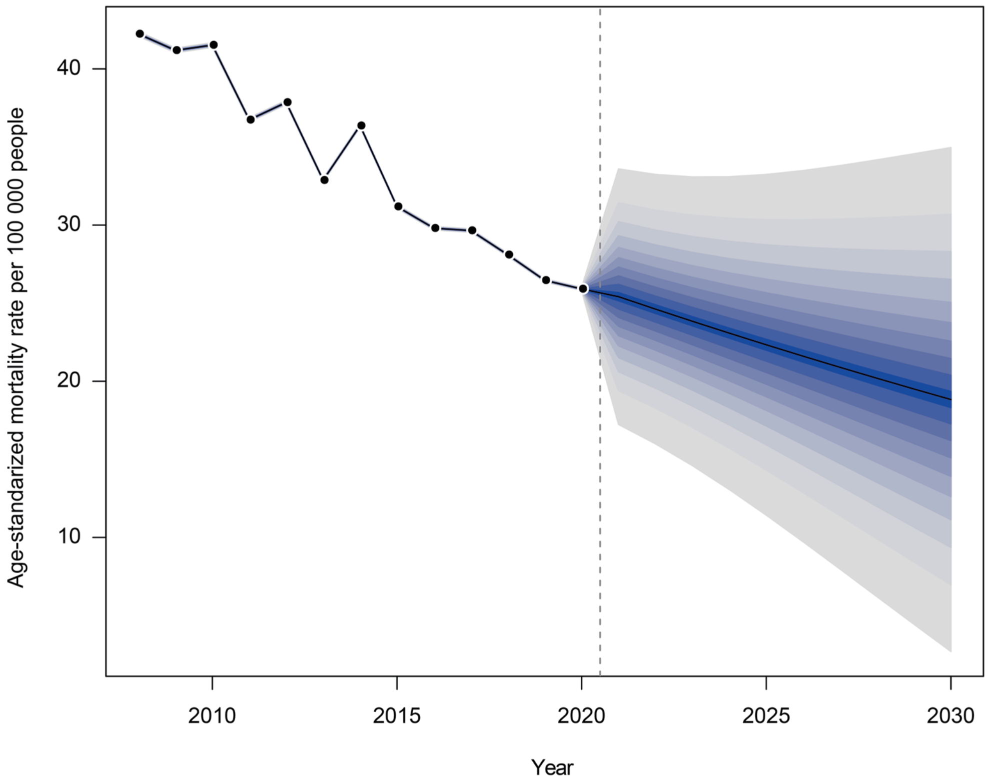

Fig. 6. Prediction of the ASMRC for liver cancer in males in 2021–2030 in China. ASMRC, the age-standardized mortality rate of China.

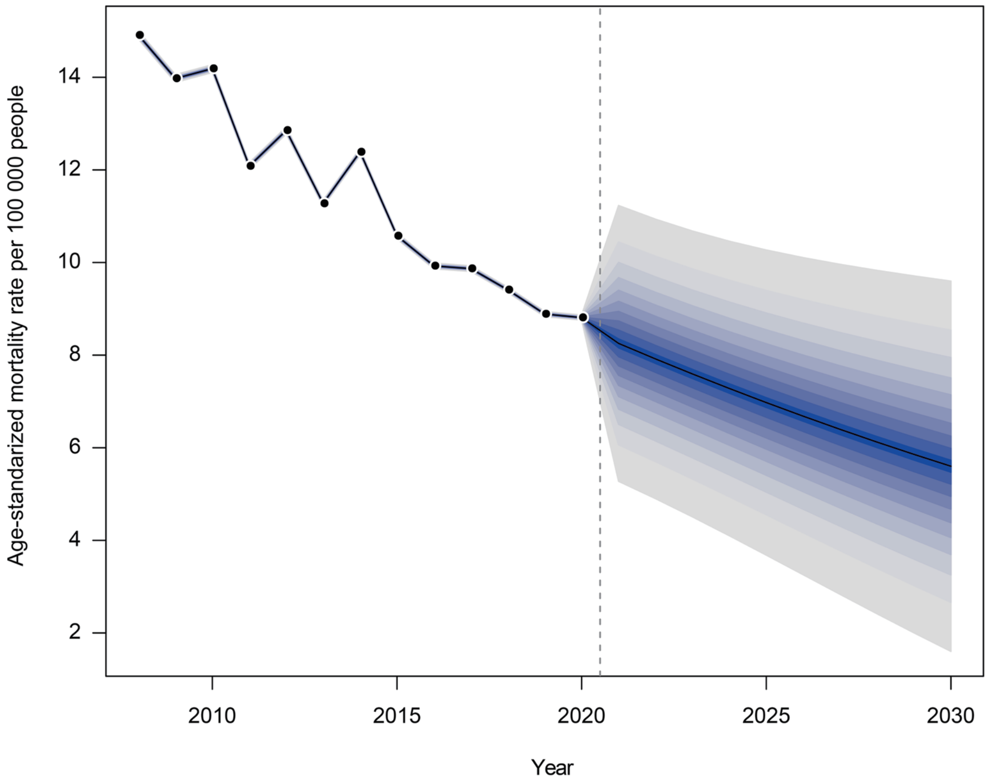

Fig. 7. Prediction of the ASMRC for liver cancer in females in 2021–2030 in China. ASMRC, the age-standardized mortality rate of China.

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Conflict of interest

LW has been an Executive Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013, HR has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2023. The other authors have no conflict of interests related to this publication.

Author contributions

Concept and design of the study (HL, XW, JQ, HR), acquisition of the data (LjW, PY), analysis and interpretation of the data (FL, LW), drafting of the manuscript (HL, XW, YW, MZ), and critical revision of the manuscript for important intellectual content (HL, XW, JQ, HR). All authors made significant contributions to this study and have approved the final manuscript.

Ethical statement

This study was approved by the Ethics Committee of National Center for Chronic and Noncommunicable Disease Control and Prevention in Chinese Center for Disease Control and Prevention (No. 202219-1). The study protocol also conformed to the ethical guidelines of the Declaration of Helsinki revised in 2013. Written informed consent was waived.

Data sharing statement

No additional data are available.

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