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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Changes in the etiology of liver cirrhosis and the corresponding management strategies

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Abstract

We read with interest the article by Xing Wang, which was published in the recent issue of the *World Journal of Hepatology* 2023; 15: 1294-1306. This article focuses particularly on the prevalence and trends in the etiology of liver cirrhosis (LC), prognosis for patients suffering from cirrhosis-related complications and hepatocellular carcinoma (HCC), and management strategies. The etiology of cirrhosis varies according to geographical, economic, and population factors. Viral hepatitis is the dominant cause in China. Vaccination and effective treatment have reduced the number of people with viral hepatitis, but the overall number is still large. Patients with viral hepatitis who progress over time to LC and HCC remain an important population to manage. The increased incidence of metabolic syndrome and alcohol consumption is likely to lead to a potential exponential increase in metabolic dysfunction-associated steatotic liver disease (MASLD)-associated LC and alcoholic liver disease in the future. Investigating the evolution of the etiology of LC is important for guiding the direction of future research and policy development. These changing trends indicate a need for greater emphasis on tackling obesity and diabetes, and implementing more effective measures to regulate alcohol consumption in order to reduce the occurrence of MASLD. In an effort to help cope with these changing trends, the authors further proposed countermeasures for healthcare authorities doctors, and patients.

Key Words: Liver cirrhosis; Etiology; Viral hepatitis; Alcoholic liver disease; Hepatocellular carcinoma; Metabolic dysfunction-associated steatotic liver disease

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Core Tip: China is aiming to eradicate viral hepatitis as a public health threat by 2030. It is expected that the prevalence of viral hepatitis will decrease in the coming years. The increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) may emerge as a leading cause of liver cirrhosis. Additionally, excessive alcohol consumption is a significant risk factor. These shifting trends necessitate innovative management strategies. There is a need for sustained implementation of measures to eliminate viral hepatitis, as well as greater efforts to control obesity, diabetes and alcohol consumption to reduce the incidence of MASLD and Alcoholic liver disease.

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INTRODUCTION

Liver cirrhosis (LC) is the final stage of progressive liver fibrosis attributed to various etiologies. The etiology of LC varies according to geographical region, economy, lifestyle, and population. Globally, hepatitis B virus (HBV) and hepatitis C virus (HCV) are the leading causes of LC and liver-related mortalities. With the development of control of HBV and cure of HCV, the prevalence of viral hepatitis has decreased. Unfortunately, LC morbidity and mortality are increasing rather than declining. The prevalence of metabolic risk factor-associated liver disease has increased substantially due to the rising prevalence of metabolic syndrome (Mets) and obesity, coupled with increased alcohol consumption and aging. It is expected that metabolic dysfunction-associated steatotic liver disease (MASLD) will soon become the leading cause of LC worldwide[1].

LC and its complications are a major public health challenge worldwide, with a significant economic and health burden. China is "leader in liver diseases"[2]. In 2017, there were 10.6 million decompensated and 112 million compensated LC cases worldwide[3]. Approximately 2 million people worldwide die from liver disease each year[4]. According to the Global Burden of Disease project, LC caused about 1 million deaths in 2010 and 1.3 million in 2016[5]. Latin America and North Africa recorded the highest LC mortality rates, while the West Coast of the Pacific and Southeast Asia had the highest number of absolute deaths[6]. LC-related complications and hepatocellular carcinoma (HCC) are the main causes of death[7]. While HBV and HCV infections are significant acquired risk factors for HCC, excessive alcohol consumption and associated conditions such as Mets, type 2 diabetes mellitus, obesity, and MASLD have also emerged as important risk factors. Liver cancer morbidity and mortality are estimated to increase by more than 20% in the coming 50 years if the rate of incidence does not decrease by at least 3% per year[8]. In the recent issue of the *World Journal of Hepatology* 2023; 15: 1294-1306[9], that study addresses an important issue: The etiology of LC in China is also changing. Viral hepatitis cirrhosis is gradually decreasing, while non-viral hepatitis cirrhosis is gradually increasing, especially alcoholic liver disease (ALD) and MASLD.

The etiology of LC differs among regions and countries. From 1990 to 2016, China's provinces had very different epidemiological patterns[10]. China is a large and rapidly growing country with a vast population. Regional disparities in the burden of LC may be attributed not only to differences in economic development and healthcare, but also to variations in the distribution of risk factors. The burden of LC also changes over time, making it essential to conduct regionalization studies to analyze the evolution of disease burden and trends in different regions. Access to localized high-quality data is crucial for developing and refining cost-effective strategies for the prevention and treatment of LC, which is necessary to address the increasing burden of chronic liver disease. Wang found that HCC and acute-on-chronic liver failure (ACLF) were identified as the strongest risk factors for in-hospital mortality[9].

ETIOLOGIES DIFFERENCES AND TEMPORAL TRENDS IN BURDEN OF LIVER CIRRHOSIS

Viral hepatitis

Viral hepatitis continues to be the leading cause of LC. Recent studies have shown that approximately 56% of HCC cases are attributed to HBV, while 20% are due to HCV[11]. The lifetime risk of HCC for HBV carriers is estimated to be 10%-25%[12], with the incidence depending on active HBV infection and/or LC. In 2016, China had approximately 12 million LC patients, with 48.9% of cases caused by HBV infection[10]. China also has the largest population of HCV-infected individuals, estimated at 9.8 million[13]. On a global scale, it is projected that chronic HCV infection will not significantly change from 2020 to 2030, but long-term outcomes such as liver-related deaths, HCC, and decompensated LC are expected to increase by 14%-17% in adults[14].

China has implemented a comprehensive strategy to prevent HBV transmission, which includes immunization, interruption of mother-to-child transmission, safe injection practices, and ensuring the safety of blood donations. Hepatitis B vaccination is recognized as the most effective tool for preventing and eliminating HBV infection. China's Hepatitis B Virus prevention policy, launched in 1985, aims to increase neonatal immunization coverage. The use of the recombinant vaccine was approved nationwide in 1992, and the HBV-free vaccination program for children under 14

years was expanded in 2002[15]. Additionally, a catch-up HBV vaccination program for children aged 8-15 was implemented during 2009-2011[16]. The success of these programs in China has led to significant population-wide health benefits, with an estimated 120 million HBV infections and 28 million chronic infections averted.

The incidence of HCV has increased dramatically in China, almost ten folds from 2003 to 2017, due to improved testing technology and government focus[2]. Direct-acting antivirals (DAA) were approved in the United States in 2013, Europe in 2014, and in China in 2017, and have proven to be effective in treating HCV infection. However, of the 15.2 million people diagnosed with HCV worldwide from 2015-2019, only 9.4 million were receiving DAA medication[7]. It is important to establish and improve appropriate surveillance mechanisms to work towards eliminating HCV.

Non-viral hepatitis

43% of the world's population currently consumes alcohol, and the global prevalence of alcohol use disorders (AUD) is 5.1% (283 million individuals)[1]. Alcohol is the primary cause of LC worldwide, with nearly 60% of cirrhosis cases in Europe, North America, and Latin America attributable to alcohol[17]. AUD tends to be more common in high-income countries, while low-income countries are likely to underreport and underdiagnose. The highest prevalence of AUD is in European countries, but the absolute burden may be higher in Asia[1]. ALD has gradually become the second leading cause of advanced liver disease in the country due to increased alcohol consumption[13]. There is a clear tendency for the rate of ALD to increase among young people and women[7]. Most of the burden of ALD falls on the 15-44 age group, representing the young and vigorous years of life[18]. Women tolerate alcohol less well than men, tend to develop ALD after lower alcohol exposure, and are more likely to have progression of ALD[19]. The proportion of female drinkers is expected to rise as the proportion of working and single women in China continues to increase. Individuals with ALD are more likely to progress to cirrhosis than those with other causes of liver diseases, including non-alcoholic fatty liver disease (NAFLD). Obesity and Mets may also act synergistically to increase the severity of all stages of ALD. Alcohol abstinence reduces deaths[20]. Therefore, reducing alcohol consumption should be prioritized in public health efforts. The World Health Organization urges countries to develop preventive policies and actions to reduce alcohol consumption and harm. China has a long history of alcohol culture, and hazardous drinking behaviors are prevalent. Alcohol has become a major contributor to the overall burden of disease in China[21]. Despite the implementation of alcohol control strategies in China since 1990, including reforms to alcohol taxation policies, restrictions on alcohol advertising, bans on drink driving, alcohol restrictions for civil servants, and monitoring underage drinking, per capita alcohol consumption has increased dramatically over the past 30 years[22]. Based on available evidence, no level of alcohol consumption can be considered safe, and in order to minimize health effects, consumption should be zero. Challenges remain for China's alcohol control public health strategy.

NAFLD, now known as MASLD, affects a quarter of adults worldwide[23]. The prevalence of NAFLD is 24%-48% in North America[24], 23%-33% in Europe[24], and 28%-32.4% in Asia[25]. NAFLD is the second leading cause of liver transplants in the United States and Europe, and the primary cause of liver disease in females[26]. Approximately 20%-30% of individuals with NAFLD will develop non-alcoholic steatohepatitis (NASH), and 10%-20% of those with NASH will develop HCC[27]. However, NAFLD-associated cirrhosis is often under-recognized or referred to as 'cryptogenic cirrhosis'. Being overweight in late adolescence has been shown to be significantly associated with an increased risk of end-stage liver disease and liver-related mortality in adulthood[28]. Metabolic risk factors emerge as the greatest threat to the health of children and adolescents. As the population ages, MASLD-associated LC is expected to grow exponentially in the coming decades[29]. Despite MASLD being an urgent public health problem, no country has yet developed a national or local public health response[30].

The prevalence of autoimmune hepatitis (AIH)[31] and primary biliary cholangitis (PBC)[32] is increasing worldwide. Reports of PBC are increasing in eastern countries[33]. There is a high prevalence in females, while males appear to have a more aggressive disease and a poorer prognosis[34]. AIH is often detected in the later stages of the disease and is associated with higher mortality. Among individuals with AIH, those with LC were more likely to develop cancer, with a 29.18-fold increased risk of HCC, particularly with prolonged immunosuppressive treatment[35]. Therefore, early diagnosis and treatment could improve the outcome of AIH-related LC.

MORTALITY AND RISK FACTORS OF LIVER CIRRHOSIS

Compensated cirrhosis is typically asymptomatic and often overlooked, but once decompensation occurs, mortality and morbidity significantly increase. The incidence of decompensation is 11% per year, but varies based on the underlying etiology[36]. ACLF is linked to organ failure and high short-term mortality in LC[37]. In the US, hospitalizations and costs related to ACLF have increased over the last decade[38]. The lowest incidence of ACLF but highest short-term mortality is observed in patients with HCV or MASLD[39]. HBV reactivation is a major predisposing factor for ACLF in China[40].

According to China Cancer Registry data, China's crude liver cancer death rate was 23.7 per 1 million in 2015[41]. Between 2020 and 2040, the number of new cases of HCC is expected to increase by 55.0%, with 1.3 million people estimated to die from HCC in 2040[8]. Effective treatment of HBV and HCV has an impact on the incidence of viral hepatitis-associated HCC. The HBV vaccination program is a key strategy to prevent HCC. A study in Taiwan reports more than 80% reduction in HCC incidence in adults vaccinated in infancy compared with the unvaccinated[42]. The annual incidence of HCC in patients with HCV-associated LC is 0.5%-10%[43]. A 70% reduction in the incidence of HCC following a sustained virological response was observed in a prospective study of French patients with HCV cirrhosis. This study suggests that DAA will play an important role in significantly reducing HCC rates in the future[44]. Increasing evidence suggests that HCC risk is increased by excessive alcohol consumption, Mets, atherosclerotic dyslipidemia, and

consumption of aflatoxin-contaminated foods, all of which can be prevented[45]. The government can reduce the incidence of HCC by focusing on risk factor prevention and comprehensive HCC surveillance.

We generally agree with the views and conclusions presented in the text, which to some extent may also reflect the trend of etiological changes in hospitalized LC patients in southern China. Additionally, we find some interesting results in the text. Looking at the temporal trends in LC etiology, the overall incidence of hepatitis B-associated LC showed a decreasing trend but peaked significantly in 2011. The possible reason is that the author's hospital is one of the leading liver disease treatment centers in southern China, and over the years it has been actively developing new technologies and treatments for hepatitis B liver failure, attracting more hepatitis B patients to come to the clinic. This phenomenon peaked in 2011-2012. The total number of hepatitis B cases began to decline in 2013, in line with the overall downward trend. When considering the characteristics of the study population over 20 years, we found that the severity of the patients' conditions lessened, in addition to being associated with an increase in quality of care, was, in our opinion, due to the following reasons: (1) With economic development, improved health insurance policies, and more convenient transportation, the awareness and attention of patients to diseases has increased, leading to more hospital admissions for mild diseases; and (2) The authors' hospitals have evolved in their specialties, expanded their wards, and relaxed their indications for hospitalization, allowing them to provide medical care to a greater number of patients and have the capacity to admit and treat more patients with relatively minor illnesses.

CLINICAL IMPLICATIONS

LC and its complications continue to pose a significant public health burden, despite some improvements in HBV and HCV. The impact of targeting the elimination of viral hepatitis is just emerging, but an increase in other risk factors may add to the overall burden of LC. National health planning should be adapted to take these changes into account, including sustainable implementation of programs to eliminate viral hepatitis, expanding screening and treatment options for HBV/HCV, primary prevention of diabetes and obesity, as well as stronger measures for controlling alcohol. It is recommended that patients with chronic liver disease should have serum aminotransferase and alpha-fetoprotein tests, liver ultrasound and elasticity tests every six months, and those with LC or HCC every three months.

Investment in the prevention, detection, and treatment of liver disease has the potential to decrease the number of deaths caused by associated liver disease, lower the incidence of complications from advanced liver disease, and reduce the associated management costs. Tracking trends of LC is essential to identify effective strategies appropriate to the local disease burden and to implement cost-effective interventions.

CONCLUSION

We are at a crucial turning point in the recognition, prevention, and treatment of liver disease. Management strategies are needed not only at the national level, but also localized policies for various regions. Early detection and treatment of cirrhosis, with a focus on ALD and NASH, and continued implementation of strategies to eliminate viral hepatitis, must be given particular attention. Establishing well-functioning and comprehensive national health systems to achieve universal coverage is crucial. For hepatologists, it is critical to increase screening of high-risk groups, identify and eliminate disease-causing factors early, and improve monitoring and follow-up with LC and HCC. For patients, maintaining good lifestyle habits, making behavioral changes, and taking necessary precautions can reduce the risks.

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