*Journal of Clinical and Translational Hepatology* **2024** vol. 12(7) | 677–684
DOI: 10.14218/JCTH.2024.00034

Review Article

# Alcoholic Liver Disease in China: A Disease Influenced by Complex Social Factors That Should Not Be Neglected

Xiaofeng Feng[1#], Nafei Huang[1#], Yuqin Wu[2], Fei Gao[1], Xiaomei Chen[2], Chenyi Zhang[2], Bing Zhang[3*] and Tao Sun[2*]

*[1]The Second Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China; [2]The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang, China; [3]Hangzhou First People's Hospital, Hangzhou, Zhejiang, China*

**Received:** January 23, 2024 | **Revised:** April 26, 2024 | **Accepted:** May 06, 2024 | **Published online:** May 31, 2024

## Abstract

Alcoholic liver disease (ALD) encompasses liver damage caused by chronic, excessive alcohol consumption. It manifests initially as marked hepatocellular steatosis and can progress to steatohepatitis, liver fibrosis, and cirrhosis. With China's rapid economic growth, coupled with a complex social background and the influence of a deleterious wine culture, the number of patients with ALD in China has increased significantly; the disease has become a social and health problem that cannot be ignored. In this review, we briefly described the social factors affecting ALD in China and elaborated on differences between alcoholic and other liver diseases in terms of complications (e.g., cirrhosis, upper gastrointestinal bleeding, hepatic encephalopathy, hepatocellular carcinoma, addiction, and other extrahepatic diseases). We also emphasized that ALD was more dangerous and difficult to treat than other liver diseases due to its complications, and that precise and effective treatment measures were lacking. In addition, we considered new ideas and treatment methods that may be generated in the future.

**Citation of this article:** Feng X, Huang N, Wu Y, Gao F, Chen X, Zhang C, *et al*. Alcoholic Liver Disease in China: A Disease Influenced by Complex Social Factors That Should Not Be Neglected. J Clin Transl Hepatol 2024;12(7):677–684. doi: 10.14218/JCTH.2024.00034.

## Introduction

Alcoholic liver disease (ALD) is caused by chronic alcohol consumption and is among the most common causes of liver-related morbidity and mortality.[1] Its incidence is increasing worldwide, placing heavy burdens on healthcare systems. ALD initially manifests as substantial hepatocyte steatosis, which can progress to steatohepatitis, liver fibrosis, and cirrhosis.[2] In the short term, severe alcoholism can also lead to acute severe alcoholic hepatitis, acute liver function damage, and even death. The underlying mechanism is complex, involving steatosis, inflammation, fibrosis, and carcinogenesis, and is the result of the combined effects of susceptibility genes, intestinal microecology, oxidative stress injury, immune injury, and programmed cell death.[3] Despite tremendous progress in research on ALD, the pathogenesis of the disease remains unclear and effective therapies remain lacking. With the rapid growth of China's economy, the continuous opening up of its society, and the difficulty of solving the social problem of "wine culture", the number of people with ALD in China has increased considerably (currently exceeding 62 million), and ALD has become a public health problem that cannot be ignored. Taking the complex social context of China as a starting point, this review compares the characteristics of ALD (cirrhosis, upper gastrointestinal bleeding, hepatic encephalopathy, hepatocellular carcinoma, addictive nature, and related extrahepatic diseases) with those of other liver diseases. In addition, we identify problems with such comparisons and propose new treatment ideas and methods for the future.

## ALD in the complex social context in China

ALD differs from some other diseases in that it is greatly influenced by social factors. The complex social context in China poses serious challenges related to ALD. For example, Chinese society has always relied on moral education in the management of underage drinking, whereas Western societies have explicitly prohibited the sale of alcohol to minors through regulations and laws. A large cross-sectional study published in 2016 indicated that alcohol use is prevalent among Chinese adolescents, with a current drinking rate of 7.3%. And 13.2% students reported having alcohol-related problems. The current data may be higher than before.[4] Moreover, Chinese people are more inclined to drink spirits than other alcoholic beverages. The top five brands in the 2021 Global Alcohol Brands spirits ranking (Maotai, Wuliangye, Yanghe, Luzhou Laojiao, and Gujing Gongjiu) are widely known in China and hold very large shares of the market. Moreover, China's unbottled alcohol market accounts for nearly 20% of its national alcohol consumption

**Keywords:** Alcoholic liver disease; Wine culture; Complication; Epidemiology; Treatment strategies; Comparison.

#Contributed equally to this work.

*__Correspondence to:__ Bing Zhang, Hangzhou First People's Hospital, No.261, Huansha Road, Hangzhou, Zhejiang 310003, China. ORCID: https://orcid.org/0009-0002-4113-397X. Tel: +86-571-85267155, Fax: +86-571-87914773, E-mail: 25413275@qq.com; Tao Sun, The Second Affiliated Hospital of Zhejiang Chinese Medical University, No.318, Chaowang Road, Gongshu District, Hangzhou, Zhejiang 310005, China. ORCID: https://orcid.org/0009-0006-5394-7865. Tel: +86-571-85267155, Fax: +86-571-88064725, E-mail: 326516058@qq.com

market, whereas overseas alcohol markets have stricter regulatory constraints and more comprehensive rules. Unbottled alcoholic beverages in China are characterized by higher alcohol contents, complexity of ingredients, and insecurity of hygiene, and thus contribute to the incidence of ALD. In addition, the influence of China's uniquely deleterious wine culture exacerbates the current state of ALD in the country. Chinese businesspeople tend to negotiate and work together while playing drinking games, and the amount of alcohol consumed represents not only the sincerity of cooperation but also, to a certain extent, the establishment of public corporate relationships. Thus, businesspeople in China are encouraged to drink excessively, whereas those in Japan, for example, are not pressured to consume alcohol and do so purely voluntarily. According to a white paper published by the China Alcoholic Beverage Association, 60% of China's drinking population is "forced to drink". The proportion of regular drinkers among Chinese adults increased from 27.0% in 2000 to 66.2% in 2015, and the WHO also estimated that 22.7% of Chinese (aged 15+years) had engaged in heavy episodic drinking in 2016.[5] From 2005 to 2016, the per-capita consumption of pure alcohol among people aged ≥ 15 years in China increased by 76%; the most recent (2022) World Health Organization (WHO) statistical report provides an average value of 6.0 L, slightly above the global average of 5.8 L.[6] In summary, we can infer that the burden of ALD in China is increasing gradually under the influence of a complex social background and a harmful alcohol consumption–based culture.

## Current status of ALD

### *Status of ALD worldwide*

Globally, 43% of the population currently consumes alcohol. Alcohol abuse has become a significant risk factor for disease, disability, and death worldwide.[7–10] The global proportions of deaths attributable to alcohol are 7.6% for men and 4.0% for women.[11] Alcohol-related diseases of different organs and injuries caused by traffic accidents and violence result in 3.3 million deaths (5.9% of all deaths) per year.[12] Alcohol-related harms particularly affect working-aged people, with 139 million disability-adjusted life years (DALYs) lost due to alcohol consumption, representing 5.1% of the total global burden of disease.[13] The global incidence of alcohol-related hepatitis has increased in recent years, especially among young people and women.[14] Alcohol is among the most common causes of end-stage liver disease, and it is implicated directly or indirectly in 50% of cirrhosis-related deaths.[15] Worldwide, ALD accounts for 4% of deaths and 5% of DALYs lost.[16] One in 10 alcohol-related deaths is due to alcohol-related cirrhosis of the liver, and nearly 50% of alcohol-related deaths are due to liver disease, equating to 225,000 DALYs lost per year.[17] According to the Global Burden of Disease study, an estimated 256,900 people died of cirrhosis and chronic liver disease in 2016, and 334,900 (27%) of these deaths were attributed to alcohol.[18] In addition, 245,000 people died of alcohol-related hepatocellular carcinoma (HCC), accounting for 30% of all HCC deaths.[19] In America, the proportion of cirrhosis cases due to alcohol consumption increased from 28% to 33% in past 10 years. And in Germany of 2018, alcohol consumption remained the dominant cause of cirrhosis, accounting for 52% of cirrhosis cases.[20]

### *Status of ALD in China*

Over the past 30 years, as the Chinese economy has continued to grow, overall alcohol consumption has increased and the status of ALD has become more severe. In China, alcohol use disorders (AUDs), which include harmful drinking patterns such as alcohol dependence and abuse, commonly develop into conditions associated with physical and mental health problems and social dysfunction. The proportion of individuals with AUDs increased dramatically from 0.45% in the mid-1980s to 3.4% in the mid-1990s, with a lifetime prevalence of 9% from 2001 to 2005.[21] Data from China in 2019 showed that alcohol consumption is a major contributor to the total disease burden, where it was the eighth-greatest contributor to disability-adjusted life-years lost.[22] According to data from the Liver Disease Center of the Chinese People's Liberation Army's 3O2 Hospital, the proportion of patients hospitalized for ALD increased from 1.7% in 2002 to 4.6% in 2013.[23] Alcohol consumption is increasing steadily in China, faster than in other countries; China is currently among the largest per-capita consumers of pure alcohol worldwide.[24] As a result, the prevalence of ALD in China (4.5%) is now comparable to that in the United States (6.2%) and European countries (6%), and higher than that in Japan (1.56–2.34%).[25–27] A meta-analysis of integrated epidemiological studies of ALD in Asia from 2000 to 2020 showed that liver cirrhosis attributed to alcohol was 12.57%.In HCC, the proportion was 8.30%.[28] The status of ALD in China is thus serious and requires increased attention.

## Why ALD should be taken seriously?

### *ALD differs from other liver diseases*

ALD encompasses alcoholic fatty liver disease, alcoholic hepatitis, steatohepatitis, liver fibrosis, cirrhosis, and liver cancer.[29] The underlying mechanism is complex, involving steatosis, inflammation, fibrosis, and carcinogenesis, and is the result of the combined effects of susceptibility genes, intestinal microecology, oxygen stress injury, immune injury, and programmed cell death.The early stage of ALD is characterized by fat accumulation in the liver and is the only stage of the disease that can be completely reversed by abstinence without drug intervention.[30] Clinically, in contrast to patients with other liver diseases, those with ALD are often characterized by combined multisystemic injury and poor compliance (Fig. 1).In addition, alcohol is a significant driver of death among patients with liver diseases or other etiologies.

### *Cirrhosis*

In recent years, the incidence of alcoholic cirrhosis has increased due to the rise in alcohol consumption in China. Alcoholic cirrhosis begins with the accumulation of fat in the liver, resulting in conditions such as steatosis and inflammation, which then develop into fibrosis and eventually lead to the degradation of the normal liver structure, culminating in irreversible disease.[13] As many patients with alcoholic cirrhosis experience symptoms and complications related to alcohol overuse, the disease is often diagnosed secondary to other conditions, such as alcoholic hepatitis with jaundice, anemia or electrolyte imbalance, pancreatitis, and infection.[31] Fibrosis is a prerequisite for the development of cirrhosis. The liver promotes hepatic fibrosis in response to alcohol through various mechanisms, such as the ethanol metabolite acetaldehyde-induced secretion of transforming growth factor-β,[32,33] lipopolysaccharide-induced activation of hematopoietic stem cells (HSCs) by activated Kupffer cells, acetaldehyde-promoted collagen production and deposition, HSC activation by activated Kupffer cells through a variety of profibrotic mediators,[34] reduction of metalloproteinase activity by reac-

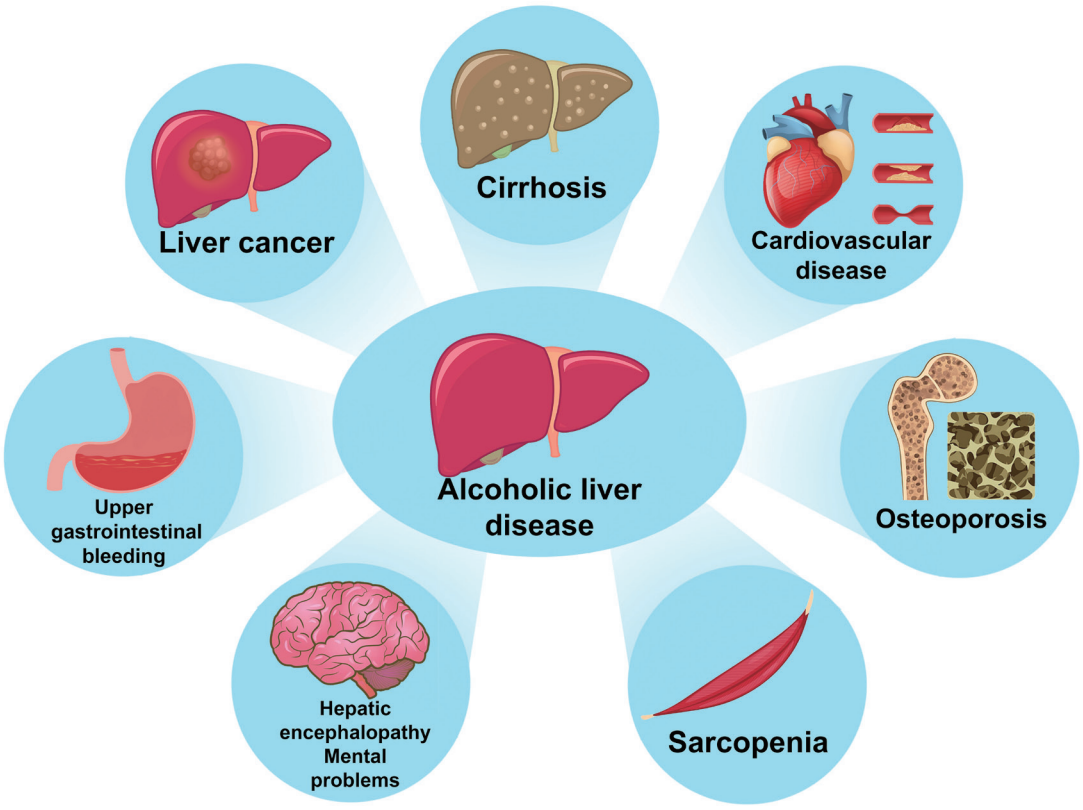


**Fig. 1. Complications associated with alcoholic liver disease.**

tive oxygen species (ROS) leading to collagen accumulation, stimulation of profibrotic HSC signaling pathways (extracellular regulated protein kinase, phosphatidylinositol 3 kinase/protein kinase B, and c-Jun N-terminal kinase) generation by ROS,[35] and production of profibrotic factors upon hepatocyte apoptosis.[36,37]

Approximately 2 billion people consume alcohol and 75 million people are diagnosed with AUDs and are at risk of alcohol-associated liver disease worldwide. Cirrhosis is currently the 11th most common cause of death globally, leading to 1.16 million deaths per year, and is among the top 20 causes of DALYs and years of life lost, accounting for 1.6% and 2.1%, respectively, of the global burden.[35] Eleven percent of all cirrhosis deaths occur in China.[38] The incidence of alcoholic cirrhosis is 10-fold greater among people with excessive alcohol use than in the non-drinking general population. The incidence rates of alcoholic liver cirrhosis among men and in the general population were 50 and 4.8 per 10,000 person-years, respectively; the equivalent rates among women were 42 and 2.3 per 10,000 person-years, respectively.[39] More than 50% of deaths associated with cirrhosis worldwide are attributable to alcohol.[15] The incidence of cirrhosis is greater in patients with ALD than in those with nonalcoholic fatty liver disease, Buga syndrome, hepatomegaly, and drug- or chemical toxicity–related cirrhosis.[40] In terms of complications, patients with alcoholic cirrhosis have significantly greater incidences of palmar erythema, spider angioma, combined ascites, and jaundice than do patients with post–hepatitis B cirrhosis.[41] In addition, aspartate transaminase/alanine transaminase ratios, which reflect liver cell damage and decreased liver function, are significantly higher in patients with alcoholic cirrhosis than in those with post–hepatitis B cirrhosis. The research of single-cell RNA transcriptomics showed that, the patients with alcoholic cirrhosis have increased ratio of intrahepatic monocyte/macrophages and a dysfunctional adaptive immune response in the liver than those with HBV-induced cirrhosis. Suggesting that the former have severe cellular and humoral immunoregulation imbalances.[42]

### *Upper gastrointestinal bleeding*

The incidence of upper gastrointestinal bleeding may be greater in patients with ALD than in those with other liver diseases due to gastric mucosal damage, portal hypertension, and gastroduodenal ulcers resulting from alcohol consumption.[43] Liver function continues to deteriorate in patients with ALD when cirrhosis progresses to the decompensated phase relative to that in patients with average cirrhosis. Alcohol consumption leads to the impairment of plasminogen synthesis and prolonged prothrombin times, causing declines in platelet and coagulation function and increasing the likelihood of acute hemorrhage development in the digestive tract.[44] Moreover, patients with alcoholic cirrhosis are more likely to develop abdominal wall varices than those with post–hepatitis B cirrhosis, possibly because alcohol acts on stellate cells in the perisinusoidal space, leading to increased resistance to blood flow in the sinusoids, which is likely to lead to upper gastrointestinal hemorrhage after alcohol abuse.[45] Patients with gastrointestinal diseases who drink alcohol are more likely than those who do not drink alcohol to experience upper-gastrointestinal-tract bleeding due to the destructive effect of ethanol on the gastric mucous membrane barrier, which exacerbates the existing gastrointestinal disease and subsequently has an erosive effect on blood ves-

sels.[46] A survey showed that the proportion of upper gastrointestinal bleeding caused by the rupture of esophageal and fundal varices due to alcoholic cirrhosis was greater than that caused by cirrhosis due to other factors (e.g., cryptogenic, autoimmune, pharmacological, and biliary) (24.5% vs. 15.4%).[47] Moreover, alcohol consumption was found to induce more upper-gastrointestinal-tract bleeding (23.5%) than did medication use (5.9%), poor diet (8.8%), and other factors (5.9%) in a group of young people.[47] Thus, the evaluation of a patient with suspected upper-gastrointestinal-tract bleeding should begin with a thorough history of the patient's medication use and social factors (alcohol, tobacco, and substance use) and physical examination.[45]

### *Hepatic encephalopathy*

Prolonged alcohol consumption can cause silent changes in the structure and function of the central and peripheral nervous systems, increasing the likelihood of developing various encephalopathies.[48] Patients with ALD have impaired liver function and a reduced ability to synthesize urea, impairing their ability to eliminate potentially toxic levels of nitrogen-containing substances, ultimately leading to an increased risk of hepatic encephalopathy.[49] The incidence of hepatic encephalopathy as a complication was found to be greater among patients with severe alcoholic hepatitis (26.1%) than among those with gastrointestinal bleeding (21.7%) and acute kidney injury (9.9%).[50] Among patients with hepatic encephalopathy, the mortality rate is significantly higher among those with histories of alcohol consumption compared to those without, and the mortality rate due to alcoholic cirrhosis (25%) is greater than that due to post–hepatitis B cirrhosis (12.7%).[51] Comparing with other liver diseases, patients with alcoholic cirrhosis had the highest risk of hepatic encephalopathy. The 1-year and 10-years cumulative HE incidences were 6.4% and 26%.[52] A survey showed that the incidence of hepatic encephalopathy was significantly higher and the improvement rate significantly lower among patients with alcoholic cirrhosis than among those with post-hepatitis cirrhosis.[53] The diagnosis of hepatic encephalopathy, whether clinically evident or not, requires clinical skill, as the disease's clinical symptoms and neuropsychological and neurophysiological manifestations are nonspecific. Thus, the diagnosis can be made only after other possible causes of brain dysfunction have been ruled out.[54]

### *Liver cancer*

In 2020, the incidence rate of primary liver cancer ranked fifth among those for malignant tumors in China, with 410,000 new cases diagnosed, and the death rate ranked second, with 391,000 deaths recorded.[55] Risk factors for liver cancer include hepatitis B and C infection, fatty liver disease, alcohol-related cirrhosis, smoking, obesity, diabetes mellitus, iron overload, and various dietary exposures. At present, alcohol is believed to cause HCC through three main mechanisms.[56] First, long-term alcohol consumption reduces the detoxification function of the liver, nutrient intake, and the body's immunity. Second, acetaldehyde, an intermediate metabolite of alcohol, is thought to promote HCC development. Third, heavy drinking may lead to alcoholic cirrhosis, which may progress to HCC.[57] The most common cause of HCC is alcohol consumption (accounting for 32–45% of cases).[58] Of all alcohol-induced deaths from malignant tumors, 80,600 [23.9%; 14,800 (16.2%) among women and 65,900 (26.8%) among men] were caused by liver cancer. Liver cancer deaths attributable to alcohol consumption were responsible for 0.2% of all deaths (0.1% among women and 0.2% among men), 10.7% of deaths from liver cancer (6.4% among women and 12.7% among men), and 1.7% of all alcohol-attributable deaths (0.9% among women and 2.1% among men).[59] Of the DALYs lost due to malignant neoplasms attributable to alcohol consumption, 2,142,000 [24.7%; 335,000 (14.9%) among women and 1,807,000 (28.2) among men] were caused by liver cancer, representing 11.2% (6.4% among women and 13.0% among men) of DALYs lost due to liver cancer. A 2.4-fold greater risk of liver cancer has been reported for individuals who drink more than one but not more than two alcoholic beverages per day on average than for individuals who do not drink alcohol, and a 3.8-fold greater relative risk has been reported for those who consume more than two alcoholic beverages per day.[60] Patients with alcohol-associated HCC usually develop the disease at a younger age and have poorer liver function and prognoses than do those with other nonviral-associated forms of HCC. Moreover, the rates of intra- and extrahepatic tumor metastasis are greater among patients with alcohol-associated HCC than among those with hepatitis B–associated HCC.[61] This HCC is usually diagnosed as a more advanced stage and consequently with a lower survival rate.[62] Bucci *et al*.[63] reported that the median overall survival time was significantly shorter for patients with alcohol-associated HCC than for those with hepatitis C–associated HCC (27.4 vs. 33.6 months).

### *Addiction*

Alcohol addiction is characterized by psychological and somatic dependence and withdrawal syndrome. Psychological dependence involves strong, uncontrollable alcohol cravings, while somatic dependence reflects biological changes in the central nervous system due to repeated alcohol consumption over long periods. A series of withdrawal symptoms occur when alcohol consumption is terminated or abruptly reduced and can only be alleviated by the repeated use of alcohol or pharmacologically similar substances.[64] Alcohol addiction has become a major risk factor for death and disability, affecting approximately 4% of the global adult population.[27] A WHO survey indicated that 3.8% of the 2 billion people worldwide who consume alcoholic beverages are diagnosed with alcohol addiction.[65] In China, for males the prevalence of alcohol dependence, alcohol abuse were 4.4% and 4.0%; the corresponding values for females were all below 0.2, 0.1.[66] Long-term alcohol consumption can cause organic brain damage resulting in personality disorders, pronounced impulsive tendencies, poor self-control, family conflict, and interpersonal tension.Moreover, alcoholic patients who have been hospitalized are prone to experience negative emotional states after discharge, which greatly facilitates the resumption of drinking, leading to a high relapse rate and representing a major challenge in the clinical treatment of alcohol addiction.[67] Relapse rates of 60–70% at 3 months and 80–90% at 1 year after treatment have been reported for individuals with alcohol dependence.[68] Abstinence from alcohol is often the first step in the treatment of ALD and is greatly complicated by alcohol addiction.

### *Other related extrahepatic diseases*

The prevalence and severity of sarcopenia are usually greater among patients with ALD than among those with other liver diseases, such as metabolism-related fatty liver disease and viral hepatitis.[69,70] Sarcopenia can occur at all stages of ALD, and its severity depends on the severity of liver disease and extent of alcohol consumption.[71] Available data indicate that 60–70% of patients with ALD have some de-

gree of sarcopenia.[69,72] In addition, ALD has different effects on bone density at various skeletal sites.[73] A large cohort study showed that hip fractures occurred five times more frequently in patients with ALD than in other patients.[74] In addition, patients with ALD are more likely than those with chronic viral hepatitis to develop osteoporosis or bone loss.[75] Moreover, the risk of cardiovascular disease is significantly increased among patients with alcohol addiction[76] and persistent heavy alcohol consumption significantly increases the risk of ischemic stroke.[77]

### *ALD is both a medical and social problem*

The irrational consumption of alcohol contributes not only to the growing burden of ALD and the increased need for medical care, but also to a societal burden. Alcohol consumption is strongly correlated with violent crime, and positively associated with fatal acts of violence in some regions.[78–80] In addition, drunk driving and accidental deaths occurring under the influence of alcohol pose significant burdens on society. In Latin America, approximately 30% of road fatalities are attributable to alcohol; and the burden of road crashes overall represented 1.5–3.9% of the gross domestic product in 2013, compared with approximately 2% in the USA.[81,82] Similarly, in China in 2015, approximately 30% of road traffic deaths, or 93,750 fatalities, were attributed to drunk driving,[83] and the offense has replaced theft as the most commonly prosecuted crime.[84] Thus, drunk driving not only consumes many social resources, but also deprives society of a significant amount of labor, thereby having a considerable societal impact.

## Treatment strategies

### *Current ALD treatment strategies and dilemmas*

According to the Guidelines for the Management of Alcoholic Liver Disease published by the Chinese Medical Association's Liver Disease Branch in 2018,[85] the principles of ALD treatment include abstinence from alcohol, nutritional support, reduction of disease severity, improvement of preexisting secondary malnutrition, and symptomatic treatment of alcoholic cirrhosis and its complications. Complete abstinence from alcohol is the primary and most basic ALD treatment, but achieving it is difficult due to alcohol addiction in people with the disease, and supporting medication may be needed. The importance of nutritional support reflects the common occurrence of malnutrition among patients with ALD and its correlation with the severity of the disease.[86] While some glucocorticosteroids and other drugs are used for ALD treatment, their therapeutic effects are unsatisfactory and vary among patients. Liver transplantation may be an option for patients who do not respond well to medication, but it is not always effective due to the limited supply of organs and the possible occurrence of post-transplantation complications. ALD treatment guidelines from China, the United States, and Europe differ in several respects. For example, China's guidelines require patients with ALD who are undergoing liver transplantation to abstain from alcohol for 3–6 months before the procedure and to have no serious alcohol-induced injury to other organs. In contrast, the European Association for the Study of the Liver (EASL) and American College of Gastroenterology (ACG) guidelines suggest that 6 months of abstinence from alcohol should no longer be considered as a requirement for transplantation because patients with severe or end-stage disease may die before achieving such abstinence.[87] In addition, while the Chinese guidelines indicate that glucocorticosteroids improve the survival rate of patients with subarachnoid hemorrhage at 28 days (but have no obvious effect at 90 days or 6 months), the EASL and ACG guidelines give clearer indications for hormone therapy, including hormone types, dosages, treatment durations, and treatment responses. The Chinese guidelines also mention various drugs, such as metadoxine and S-adenosylmethionine, for which additional evidence is needed.[87] Regional ALD guidelines need to be developed based on evidence-based medicine and population characteristics.

## Future solutions

### *Regulation of drinking behavior*

The WHO has led a series of initiatives to reduce alcohol consumption worldwide, three of which are considered to be the most cost-effective policies: taxation, supply reduction, and restrictions on promotion. Alcohol consumption can be further reduced by regulating the hours of sale, controlling the issuance of alcohol licenses, and establishing a legal age of purchase, among other measures.[20] China has not taken such measures, and their implementation can be considered from the perspective of government legislation.

### *Intestinal probiotic therapy*

The gut microbial community is closely associated with ALD and is involved in pathological processes such as hepatocellular steatosis, steatohepatitis, liver fibrosis, cirrhosis, and HCC.[88] Growing evidence indicates that alcohol intake leads to major changes in the gut microbial composition and the loss of gut barrier function, thereby accelerating the progression of alcohol-induced liver injury.[89] In recent years, probiotics have been found to have protective and palliative effects on various complications of ALD, and many approaches have been explored to modulate and restore the gut microbiota in patients with ALD and improve microbiota–gut–liver–brain axis communication as a way of decreasing alcohol intake and slowing the progression of the disease.[90] The future development of novel probiotic strains and related products will hopefully provide additional options for the treatment of different stages of ALD. The effectiveness and safety of new probiotic preparations will need to be confirmed.

### *Traditional Chinese medicine*

Many traditional Chinese medicine scholars, who have adopted holistic concepts of diagnosis and treatment and base medicinal prescription on their own clinical experience and rationale, have reported great benefits in the treatment of ALD. Natural traditional Chinese medicines play important roles in the treatment of this disease due to their multiple targets, potency, and low risk of side effects. Some traditional Chinese medicine monomers, their extracts, and combinations have been shown to effectively prevent the pathogenesis of ALD and to be useful in its treatment. For example, Qiu *et al*.[91] reported that *Hovenia dulcis* extract ameliorated chronic alcoholic liver injury in rats, and Liu *et al*.[92] reported that *Pueraria lobata* shows good efficacy in the initial treatment of ALD. In addition, clinical studies have shown that Zhi-Zi-Da-Huang decoction was effective in the treatment of ALD by antioxidant mechanism.[93] Other studies have shown that Xie-Zhuo-Tiao-Zhi formula can alleviate alcohol-induced liver injury, oxidative stress, and inflammation possibly through modulation of Nrf2/Keap1 and MAPKs/NF-κB signaling pathways.[94] In the treatment of ALD, whether it is staged or based on type or evidence, traditional Chinese medicine thus has better effects. Tradi-

tional Chinese medicine can not only relieve patients' pain, but also improve their quality of life, and its use to treat ALD in the future would be a very promising direction.

## Summary

Under the influence of many social factors, the number of Chinese patients with ALD is increasing annually. ALD has more complications than other liver diseases and is more dangerous. At present, China's system for the diagnosis and treatment of this disease is imperfect, and effective drugs and attention from doctors, patients, and society are lacking. Thus, additional research on ALD is needed.

## Funding

This review was supported by Science and Technology Department of National Administration of Traditional Chinese Medicine-Administration of Traditional Chinese Medicine of Zhejiang Province Jointly Established Science and Technology Plan Project, Project No. GZY-ZJ-KJ-24071.

## Conflict of interest

The authors have no conflict of interests related to this publication.

## Author contributions

Writing the original draft (XF, NH); review and editing (YW, XC); literature research (FG, CZ); and conceptualization and funding acquisition (TS, BZ). All authors have read and approved the final version of the manuscript.

## References

[1] Wu X, Fan X, Miyata T, Kim A, Cajigas-Du Ross CK, Ray S, *et al*. Recent Advances in Understanding of Pathogenesis of Alcohol-Associated Liver Disease. Annu Rev Pathol 2023;18:411–438. doi:10.1146/annurev-pathmechdis-031521-030435, PMID:36270295.
[2] Huang DQ, Mathurin P, Cortez-Pinto H, Loomba R. Global epidemiology of alcohol-associated cirrhosis and HCC: trends, projections and risk factors. Nat Rev Gastroenterol Hepatol 2023;20(1):37–49. doi:10.1038/s41575-022-00688-6, PMID:36258033.
[3] Yan C, Hu W, Tu J, Li J, Liang Q, Han S. Pathogenic mechanisms and regulatory factors involved in alcoholic liver disease. J Transl Med 2023;21(1):300. doi:10.1186/s12967-023-04166-8, PMID:37143126.
[4] Guo L, Deng JX, He Y, Deng XQ, Huang JH, Huang GL, *et al*. Alcohol use and alcohol-related problems among adolescents in China: A large-scale cross-sectional study. Medicine 2016;95(38):e4533. doi:10.1097/md.0000000000004533, PMID:27661013.
[5] Hu AQ, Jiang H, Rowan D, Guo L, Zhao XX, Hao W, *et al*. The transition of alcohol control in China 1990-2019: Impacts and recommendations. Int J Drug Policy 2022;105:103698. doi:10.1016/j.drugpo.2022.103698, PMID:35483250.
[6] World Health Organization. Global status report on alcohol and health 2018. Available from https://apps.who.int/iris/handle/10665/274603. October, 27 2021.
[7] Rehm J. The risks associated with alcohol use and alcoholism. Alcohol Res Health 2011;34(2):135–43. PMID:22330211.
[8] GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392(10152):1015–1035. doi:10.1016/S0140-6736(18)31310-2, PMID:30146330.
[9] Meza V, Arnold J, Díaz LA, Ayala Valverde M, Idalsoaga F, Ayares G, *et al*. Alcohol Consumption: Medical Implications, the Liver and Beyond. Alcohol Alcohol 2022;57(3):283–291. doi:10.1093/alcalc/agac013, PMID:35333295.
[10] Williams R, Aspinall R, Bellis M, Camps-Walsh G, Cramp M, Dhawan A, *et al*. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Lancet 2014;384(9958):1953–1997. doi:10.1016/S0140-6736(14)61838-9, PMID:25433429.
[11] Mendis S, Davis S, Norrving B. Organizational update: the world health organization global status report on noncommunicable diseases 2014; one more landmark step in the combat against stroke and vascular disease. Stroke 2015;46(5):e121–e122. doi:10.1161/STROKEAHA.115.008097, PMID:25873596.
[12] Rehm J, Taylor B, Mohapatra S, Irving H, Baliunas D, Patra J, *et al*. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. Drug Alcohol Rev 2010;29(4):437–445. doi:10.1111/j.1465-3362.2009.00153.x, PMID:20636661.
[13] Hosseini N, Shor J, Szabo G. Alcoholic Hepatitis: A Review. Alcohol Alcohol 2019;54(4):408–416. doi:10.1093/alcalc/agz036, PMID:31219169.
[14] Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. J Hepatol 2023;79(2):516–537. doi:10.1016/j.jhep.2023.03.017, PMID:36990226.
[15] Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019;70(1):151–171. doi:10.1016/j.jhep.2018.09.014, PMID:30266282.
[16] Mitra S, De A, Chowdhury A. Epidemiology of non-alcoholic and alcoholic fatty liver diseases. Transl Gastroenterol Hepatol 2020;5:16. doi:10.21037/tgh.2019.09.08, PMID:32258520.
[17] Mokdad AH, Forouzanfar MH, Daoud F, Mokdad AA, El Bcheraoui C, Moradi-Lakeh M, *et al*. Global burden of diseases, injuries, and risk factors for young people's health during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2016;387(10036):2383–2401. doi:10.1016/S0140-6736(16)00648-6, PMID:27174305.
[18] GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390(10100):1151–1210. doi:10.1016/S0140-6736(17)32152-9, PMID:28919116.
[19] Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, *et al*. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. JAMA Oncol 2017;3(12):1683–1691. doi:10.1001/jamaoncol.2017.3055, PMID:28983565.
[20] Huang DQ, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, *et al*. Global epidemiology of cirrhosis-aetiology, trends and predictions. Nat Rev Gastroenterol Hepatol 2023;20(6):388–398. doi:10.1038/s41575-023-00759-2, PMID:36977794.
[21] Tang YL, Xiang XJ, Wang XY, Cubells JF, Babor TF, Hao W. Alcohol and alcohol-related harm in China: policy changes needed. Bull World Health Organ 2013;91(4):270–276. doi:10.2471/BLT.12.107318, PMID:23599550.
[22] GBD 2019 Risk Factors. Collaborators Global burden of 87 risk factors in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020;396(10258):1223–1249. doi:10.1016/s0140-6736(20)30752-2, PMID:33069327.
[23] Huang AG, Chang BX, Sun Y, Lin HM, Li BS, Teng GJ, *et al*. Disease spectrum of alcoholic liver disease in Beijing 302 Hospital from 2002 to 2013: A large tertiary referral hospital experience from 7422 patients. Medicine (Baltimore) 2017;96(7):e6163. doi:10.1097/MD.0000000000006163, PMID:28207552.
[24] Xiao J, Wang F, Wong NK, He JH, Zhang R, Sun RJ, *et al*. Global liver disease burdens and research trends: Analysis from a Chinese perspective. J Hepatol 2019;71(1):212–221. doi:10.1016/j.jhep.2019.03.004, PMID:30871980.
[25] Fan JG. Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. J Gastroenterol Hepatol 2013;28(Suppl 1):11–17. doi:10.1111/jgh.12036, PMID:23855290.
[26] Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 2009;373(9682):2223–2233. doi:10.1016/S0140-6736(09)60746-7, PMID:19560604.
[27] Lipari RN, Williams MR, Copello EAP, Pemberton MR. Risk and Protective Factors and Estimates of Substance Use Initiation: Results from the 2015 National Survey on Drug Use and Health. CBHSQ Data Review. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2012. PMID:29792622.
[28] Xu H, Xiao P, Zhang F, Liu T, Gao Y. Epidemic characteristics of alcohol-related liver disease in Asia from 2000 to 2020: A systematic review and meta-analysis. Liver Int 2022;42(9):1991–1998. doi:10.1111/liv.15312, PMID:35593004.
[29] Dunn W, Shah VH. Pathogenesis of Alcoholic Liver Disease. Clin Liver Dis 2016;20(3):445–456. doi:10.1016/j.cld.2016.02.004, PMID:27373608.
[30] Kong LZ, Chandimali N, Han YH, Lee DH, Kim JS, Kim SU, *et al*. Pathogenesis, Early Diagnosis, and Therapeutic Management of Alcoholic Liver Disease. Int J Mol Sci 2019;20(11):2712. doi:10.3390/ijms20112712, PMID:31159489.
[31] Singh VK, Yadav D, Garg PK. Diagnosis and Management of Chronic Pancreatitis: A Review. JAMA 2019;322(24):2422–2434. doi:10.1001/jama.2019.19411, PMID:31860051.
[32] Svegliati-Baroni G, Inagaki Y, Rincon-Sanchez AR, Else C, Saccomanno S, Benedetti A, *et al*. Early response of alpha2(I) collagen to acetaldehyde in human hepatic stellate cells is TGF-beta independent. Hepatology 2005;42(2):343–352. doi:10.1002/hep.20798, PMID:16025520.
[33] Roehlen N, Crouchet E, Baumert TF. Liver Fibrosis: Mechanistic Concepts and Therapeutic Perspectives. Cells 2020;9(4):E875. doi:10.3390/cells9040875, PMID:32260126.
[34] Bataller R, Brenner DA. Liver fibrosis. J Clin Invest 2005;115(2):209–218. doi:10.1172/JCI24282, PMID:15690074.
[35] Arthur MJ, Iredale JP, Mann DA. Tissue inhibitors of metalloproteinases: role in liver fibrosis and alcoholic liver disease. Alcohol Clin Exp Res 1999;23(5):940–943. doi:10.1111/j.1530-0277.1999.tb04208.x, PMID:10371419.
[36] Pastorino JG, Shulga N, Hoek JB. TNF-alpha-induced cell death in ethanol-exposed cells depends on p38 MAPK signaling but is independent of Bid and caspase-8. Am J Physiol Gastrointest Liver Physiol 2003;285(3):G503–

G516. doi:10.1152/ajpgi.00442.2002, PMID:12748063.
[37] Wheeler MD, Kono H, Yin M, Nakagami M, Uesugi T, Arteel GE, *et al*. The role of Kupffer cell oxidant production in early ethanol-induced liver disease. Free Radic Biol Med 2001;31(12):1544–1549. doi:10.1016/s0891-5849(01)00748-1, PMID:11744328.
[38] Mokdad AA, Lopez AD, Shahraz S, Lozano R, Mokdad AH, Stanaway J, *et al*. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med 2014;12:145. doi:10.1186/s12916-014-0145-y, PMID:25242656.
[39] Askgaard G, Leon DA, Kjaer MS, Deleuran T, Gerds TA, Tolstrup JS. Risk for alcoholic liver cirrhosis after an initial hospital contact with alcohol problems: A nationwide prospective cohort study. Hepatology 2017;65(3):929–937. doi:10.1002/hep.28943, PMID:27862159.
[40] Toshikuni N, Tsutsumi M, Arisawa T. Clinical differences between alcoholic liver disease and nonalcoholic fatty liver disease. World J Gastroenterol 2014 14 20(26):8393–8406. doi:10.3748/wjg.v20.i26.8393, PMID:25024597.
[41] Bao CN, Li CY, Meng H, Bai TY, Shi Y. Comparative analysis of clinical characteristics of patients with alcoholic cirrhosis and post-hepatitis B cirrhosis. Da Lian Yi Ke Da Xue Xue Bao 2022;44(03):207–212. doi:10.11724/jdmu.2022.03.04.
[42] Zhang PP, Li H, Peng B, Zhang Y, Liu K, Cheng K, *et al*. Single-cell RNA transcriptomics reveals differences in the immune status of alcoholic and hepatitis B virus-related liver cirrhosis. Front Endocrinol (Lausanne) 2023;14:1132085. doi:10.3389/fendo.2023.1132085, PMID:36817578.
[43] Auroux J, Lamarque D, Roudot-Thoraval F, Deforges L, Chaumette MT, Richardet JP, *et al*. Gastroduodenal ulcer and erosions are related to portal hypertensive gastropathy and recent alcohol intake in cirrhotic patients. Dig Dis Sci 2003;48(6):1118–1123. doi:10.1023/a:1023772930681, PMID:12822873.
[44] Niraj B, Aparna, Anupam P, Anita N, Abhishek K. Coagulation Profile and its Correlation with Severity of Liver Dysfunction and Gastrointestinal Bleed in Alcoholic Liver Disease Patients. J Assoc Physicians India 2021;69(6):11–12. PMID:34472786.
[45] Lucey MR. Alcohol-Associated Cirrhosis. Clin Liver Dis 2019;23(1):115–126. doi:10.1016/j.cld.2018.09.013, PMID:30454826.
[46] Andersen IB, Jorgensen T, Bonnevie O, Gronbaek M, Sorensen TI. Smoking and alcohol intake as risk factors for bleeding and perforated peptic ulcers: a population-based cohort study. Epidemiology 2000;11(4):434–9. doi:10.1097/00001648-200007000-00012, PMID:10874551.
[47] Zhang YJ. Epidemiological investigation of upper gastrointestinal bleeding: single-center study and systematic analysis of Chinese literature [Dissertation]. Luzhou: Southwest Medical University; 2018.
[48] Hammoud N, Jimenez-Shahed J. Chronic Neurologic Effects of Alcohol. Clin Liver Dis 2019;23(1):141–155. doi:10.1016/j.cld.2018.09.010, PMID:30454828.
[49] Glavind E, Aagaard NK, Grønbæk H, Møller HJ, Orntoft NW, Vilstrup H, *et al*. Alcoholic Hepatitis Markedly Decreases the Capacity for Urea Synthesis. PLoS One 2016;11(7):e0158388. doi:10.1371/journal.pone.0158388, PMID:27379798.
[50] Dong JL, Zhang L, Dong PL, Chen Y. Analysis of clinical characteristics and prognosis of patients with severe alcoholic hepatitis. Zhong Guo Yi Xue Qian Yan Za Zhi 2023;15(02):38–45. doi:10.12037/YXQY.2023.02-06.
[51] Liu YY. Analysis of clinical characteristics and prognostic factors of hepatic encephalopathy [Dissertation]. Dalian: Dalian Medical University; 2020 . doi:10.26994/d.cnki.gdlyu.2019.000885.
[52] Mohamed IE, Vinod KR. Epidemiology of Hepatic Encephalopathy.Clin Liver Dis. 2020;24(2):157–174. doi:10.1016/j.cld.2020.01.001, PMID:32245524.
[53] Herbert DN. Hepatic Encephalopathy in Liver Cirrhosis. J Transl Int Med 2017;5(1):64–67. doi:10.1515/jtim-2017-0013, PMID:28680841.
[54] Weissenborn K. Hepatic Encephalopathy: Definition, Clinical Grading and Diagnostic Principles. Drugs 2019;79(Suppl 1):5–9. doi:10.1007/s40265-018-1018-z, PMID:30706420.
[55] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71(3):209–249. doi:10.3322/caac.21660, PMID:33538338.
[56] He F, Sha Y, Wang B. Relationship between alcohol consumption and the risks of liver cancer, esophageal cancer, and gastric cancer in China: Meta-analysis based on case-control studies. Medicine (Baltimore) 2021;100(33):e26982. doi:10.1097/MD.0000000000026982, PMID:34414976.
[57] Zimmerlin L, Donnenberg VS, Rubin JP, Donnenberg AD. Mesenchymal markers on human adipose stem/progenitor cells. Cytometry A 2013;83(1):134–140. doi:10.1002/cyto.a.22227, PMID:23184564.
[58] Testino G, Leone S, Borro P. Alcohol and hepatocellular carcinoma: a review and a point of view. World J Gastroenterol 2014;20(43):15943–15954. doi:10.3748/wjg.v20.i43.15943, PMID:25473148.
[59] Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. J Hepatol 2013;59(1):160–168. doi:10.1016/j.jhep.2013.03.007, PMID:23511777.
[60] Ioannou GN, Weiss NS, Kowdley KV. Relationship between transferrin-iron saturation, alcohol consumption, and the incidence of cirrhosis and liver cancer. Clin Gastroenterol Hepatol 2007;5(5):624–629. doi:10.1016/j.cgh.2007.01.008, PMID:17478349.
[61] Zeng LP, Zhao XF, Spandler C, Mavrogenes JA, Mernagh TP, Liao W, *et al*. The role of iron-rich hydrosaline liquids in the formation of Kiruna-type iron oxide-apatite deposits. Sci Adv 2024;10(17):eadk2174. doi:10.1126/sciadv.adk2174, PMID:38657067.
[62] Helena HE, Natalia JE, Elisa P, Ramon B. Alcohol-associated liver disease: Epidemiology and management. Ann Hepatol 2024;29(1):101162. doi:10.1016/j.aohep.2023.101162, PMID:37832648.
[63] Bucci L, Garuti F, Camelli V, Lenzi B, Farinati F, Giannini EG, *et al*. Comparison between alcohol- and hepatitis C virus-related hepatocellular carcinoma: clinical presentation, treatment and outcome. Aliment Pharmacol Ther 2016;43(3):385–399. doi:10.1111/apt.13485, PMID:26662476.
[64] Chick J, Andersohn F, Guillo S, Borchert K, Toussi M, Braun S, *et al*. Safety and Persistence of Nalmefene Treatment for Alcohol Dependence. Results from Two Post-authorisation Safety Studies. Alcohol Alcohol 2021;56(5):556–564. doi:10.1093/alcalc/agab045, PMID:34196359.
[65] Rastogi A, Manthey J, Wiemker V, Probst C. Alcohol consumption in India: a systematic review and modelling study for sub-national estimates of drinking patterns. Addiction 2022;117(7):1871–1886. doi:10.1111/add.15777, PMID:34873774.
[66] Cheng HG, Deng F, Wei X, Michael RP. Prevalence of alcohol use disorders in mainland China: a systematic review. Addiction 2015;110(5):761–74. doi:10.1111/add.12876, PMID:25678403.
[67] Seo D, Sinha R. Neuroplasticity and Predictors of Alcohol Recovery. Alcohol Res 2015;37(1):143–52. PMID:26259094.
[68] Seo S, Mohr J, Beck A, Wüstenberg T, Heinz A, Obermayer K. Predicting the future relapse of alcohol-dependent patients from structural and functional brain images. Addict Biol 2015;20(6):1042–1055. doi:10.1111/adb.12302, PMID:26435383.
[69] Dasarathy J, McCullough AJ, Dasarathy S. Sarcopenia in Alcoholic Liver Disease: Clinical and Molecular Advances. Alcohol Clin Exp Res 2017;41(8):1419–1431. doi:10.1111/acer.13425, PMID:28557005.
[70] Steiner JL, Lang CH. Dysregulation of skeletal muscle protein metabolism by alcohol. Am J Physiol Endocrinol Metab 2015;308(9):E699–E712. doi:10.1152/ajpendo.00006.2015, PMID:25759394.
[71] McClain CJ, Barve SS, Barve A, Marsano L. Alcoholic liver disease and malnutrition. Alcohol Clin Exp Res 2011;35(5):815–820. doi:10.1111/j.1530-0277.2010.01405.x, PMID:21284673.
[72] Dasarathy S. Nutrition and Alcoholic Liver Disease: Effects of Alcoholism on Nutrition, Effects of Nutrition on Alcoholic Liver Disease, and Nutritional Therapies for Alcoholic Liver Disease. Clin Liver Dis 2016;20(3):535–550. doi:10.1016/j.cld.2016.02.010, PMID:27373615.
[73] Jelena J, Petar M, Danica C, Miomira I, Nada T, Milos B, *et al*. Mechanostructural alteration in proximal femora of individuals with alcoholic liver disease: Implications for increased bone fragility. Bone 2021;150:116020. doi:10.1016/j.bone.2021.116020, PMID:34044170.
[74] Otete H, Deleuran T, Fleming KM, Card T, Aithal GP, Jepsen P, *et al*. Hip fracture risk in patients with alcoholic cirrhosis: A population-based study using English and Danish data. J Hepatol 2018;69(3):697–704. doi:10.1016/j.jhep.2018.04.002, PMID:29673756.
[75] Zheng JP, Miao HX, Zheng SW, Liu WL, Chen CQ, Zhong HB, *et al*. Risk factors for osteoporosis in liver cirrhosis patients measured by transient elastography. Medicine (Baltimore) 2018;97(20):e10645. doi:10.1097/MD.0000000000010645, PMID:29768330.
[76] Hvidtfeldt UA, Frederiksen ME, Thygesen LC, Kamper-Jørgensen M, Becker U, Grønbaek M. Incidence of cardiovascular and cerebrovascular disease in Danish men and women with a prolonged heavy alcohol intake. Alcohol Clin Exp Res 2008;32(11):1920–1924. doi:10.1111/j.1530-0277.2008.00776.x, PMID:18715276.
[77] Jeong SM, Lee HR, Han K, Jeon KH, Kim D, Yoo JE, *et al*. Association of Change in Alcohol Consumption With Risk of Ischemic Stroke. Stroke 2022;53(8):2488–2496. doi:10.1161/STROKEAHA.121.037590, PMID:35440171.
[78] Norström T. Alcohol and homicide in the United States: is the link dependent on wetness? Drug Alcohol Rev 2011;30(5):458–465. doi:10.1111/j.1465-3362.2011.00295.x, PMID:21896067.
[79] Proescholdt MG, Walter M, Wiesbeck GA. [Alcohol and violence: a current review]. Fortschr Neurol Psychiatr 2012;80(8):441–449. doi:10.1055/s-0031-1282018, PMID:22431128.
[80] Ramstedt M. Population drinking and homicide in Australia: a time series analysis of the period 1950-2003. Drug Alcohol Rev 2011;30(5):466–472. doi:10.1111/j.1465-3362.2011.00322.x, PMID:21896068.
[81] Lefio Á, Bachelet VC, Jiménez-Paneque R, Gomolán P, Rivas K. A systematic review of the effectiveness of interventions to reduce motor vehicle crashes and their injuries among the general and working populations. Rev Panam Salud Publica 2018;42:e60. doi:10.26633/RPSP.2018.60, PMID:31093088.
[82] Chikritzhs T, Livingston M. Alcohol and the Risk of Injury. Nutrients 2021;13(8):2777. doi:10.3390/nu13082777, PMID:34444939.
[83] Xiao W, Ning P, Schwebel DC, Hu G. Evaluating the Effectiveness of Implementing a More Severe Drunk-Driving Law in China: Findings from Two Open Access Data Sources. Int J Environ Res Public Health 2017;14(8):832. doi:10.3390/ijerph14080832, PMID:28757551.
[84] Wu Zifang. Group work intervention study on community correction of drunk driving prisoners [Dissertation]. Shaanxi: Northwest A & F University; 2022. doi:10.27409/d.cnki.gxbnu.2021.000987.
[85] Li YM, Fan JG. Guidelines of prevention and treatment for alcoholic liver disease (2018, China). J Dig Dis 2019;20(4):174–180. doi:10.1111/1751-2980.12687, PMID:30450822.
[86] Singh S, Osna NA, Kharbanda KK. Treatment options for alcoholic and non-alcoholic fatty liver disease: A review. World J Gastroenterol 2017;23(36):6549–6570. doi:10.3748/wjg.v23.i36.6549, PMID:29085205.
[87] Yang S, Xing HC, Cheng J. Comparison and interpretation of Chinese, American, and European guidelines on alcoholic liver diseases. Lin Chuang Gan Dan Bing Za Zhi 2018;34(07):1420–1422. doi:10.3969/j.issn.1001-5256.2018.07.011.
[88] Zhang DY, Liu ZJ, Bai FH. Roles of Gut Microbiota in Alcoholic Liver Disease. Int J Gen Med 2023;16:3735–3746. doi:10.2147/IJGM.S420195, PMID:37641627.
[89] Jew MH, Hsu CL. Alcohol, the gut microbiome, and liver disease. J Gastroen-

terol Hepatol 2023;38(8):1205–1210. doi:10.1111/jgh.16199, PMID:37096652.
[90] Fuenzalida C, Dufeu MS, Poniachik J, Roblero JP, Valenzuela-Pérez L, Beltrán CJ. Probiotics-Based Treatment as an Integral Approach for Alcohol Use Disorder in Alcoholic Liver Disease. Front Pharmacol 2021;12:729950. doi:10.3389/fphar.2021.729950, PMID:34630107.
[91] Qiu P, Dong Y, Zhu T, Luo YY, Kang XJ, Pang MX, *et al*. Semen hoveniae extract ameliorates alcohol-induced chronic liver damage in rats via modulation of the abnormalities of gut-liver axis. Phytomedicine 2019;52:40–50. doi:10.1016/j.phymed.2018.09.209, PMID:30599911.
[92] Liu YS, Yuan MH, Zhang CY, Liu HM, Liu JR, Wei AL, *et al*. Puerariae Lobatae radix flavonoids and puerarin alleviate alcoholic liver injury in zebrafish by regulating alcohol and lipid metabolism. Biomed Pharmacother 2021;134:111121. doi:10.1016/j.biopha.2020.111121, PMID:33341668.
[93] Li A, Fang F. Network pharmacology-based antioxidant effect study of zhi-zi-da-huang decoction for alcoholic liver disease. Evid Based Complement Alternat Med 2015;2015:492470. doi:10.1155/2015/492470, PMID:2592261.
[94] Chang KX, Guo R, Hu WB, Wang XZ, Cao FW, Qiu JN, *et al*. Xie Zhuo Tiao Zhi formula ameliorates chronic alcohol-induced liver injury in mice. Front Pharmacol 2024;15:1363131. doi:10.3389/fphar.2024.1363131, PMID:38681193.