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REVIEW

Growing burden of alcoholic liver disease in China: A review

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Abstract

Explosive economic growth and increasing social openness in China over the last 30 years have significantly boosted alcohol consumption, and consequently, the incidence of alcoholic liver disease (ALD) in China has increased. Because the epidemiologic and clinical features of ALD in the Chinese population may differ from those of the Caucasian population, this review describes the epidemiology, pathogenesis, genetic polymorphisms, diagnosis, and treatment of ALD in the Chinese population. This updated knowledge of ALD in China provides information needed for a global understanding of ALD and may help in the development of useful strategies for reducing the global ALD burden.

Key words: Alcoholic liver disease; Epidemiology; Morbidity; China

Core tip: Explosive economic growth and increasing social openness in China over the last 30 years have significantly boosted alcohol consumption, and consequently, the incidence of alcoholic liver disease (ALD) in China has increased. This review describes the epidemiology, pathogenesis, genetic polymorphisms, diagnosis, and treatment of ALD in the Chinese population, with the goal of supporting the development of useful strategies for reducing the global ALD burden.

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INTRODUCTION

The incidence of different chronic liver diseases as well as the number of patients afflicted in China have changed significantly in the past three decades. Chronic hepatitis B was once a dominant chronic liver disease in China, but the frequency of hepatitis B virus (HBV) infection has been dramatically reduced to 1% or less among children younger than 10 years old with successful implementation of the Expanded Program on Immunization for HBV initiated in 1992 and later the universal HBV vaccination program in China. Although the management of chronic HBV-related liver diseases in China remains a daunting task, the prevalence of other chronic liver diseases, notably alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD), is rapidly increasing[1].

Alcohol consumption in developed countries is a costly health problem, but the trend has been steady during the last 30 years. In contrast, as many developing countries have experienced significant economic expansion, a byproduct has been an alarming rise in alcohol consumption, as reflected by increased alcohol production. For example, in China, beer production increased by 2.27 times over 18 years from 1987.67 tons in 1998 to 4506.44 tons in 2016[2-5]. Moreover, the percentage of the Chinese population that reported weekly regular alcohol drinking increased by more than 33% between 2004 and 2008[6]. The annual consumed volume of alcoholic beverages per capita in the general Chinese population increased from 4.9 L in 2003-2005 to 7.2 L in 2016, with regular Chinese drinkers consuming an average of 12.9 L *per capita* in 2016[7]. By 2013, China was globally ranked as the second heaviest drinking country only second to the United Kingdom[8]. In addition, rapid economic development and improved living standards have brought profound changes in diet structure and lifestyle among the Chinese people, with a notable consequence being an increase in the frequency of NAFLD[9,10].

Excessive alcohol drinking is a leading cause of chronic liver disease and induces a wide range of liver pathologies from simple steatosis to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). In 2010, about half a million deaths globally were attributable to alcoholic cirrhosis, which accounted for 47.9% of all cirrhosis-related mortalities, and alcohol-related HCC caused an additional 80000 deaths[11]. Approximately 75% of all cases of liver cancer in the world occur in Asia, and China alone bears > 50% of the global liver cancer burden[12]. In 2005, ALD was responsible for 23.4% of liver cancer-related deaths in men and 2.2% of such deaths in women in China[13]. The number of deaths caused by liver cancer due to alcohol use among all ages and the age-standardized death rate per 100000 people in China were 45333 (95%UI: 39927-50465) and 6.02 (95%UI: 5.34-6.67) in 1990, compared with 25665 (95%UI: 21358-30338) and 1.87 (95%UI: 1.57-2.20) in 2013, respectively[14]. In contrast, alcohol-induced liver cancer ranks first among all causes of liver cancer mortality, accounting for 53%, 46%, 42%, 39%, and 37% of cases in Eastern Europe, Central Europe, Southern Latin America, Australasia, and, high-income North America, respectively[15]. Chronic heavy alcohol consumption may trigger and promote HCC though the generation of carcinogenic aldehydes, reactive oxygen species (ROS), damage-associated molecular patterns (DAMPs), and pathogen-associated molecular patterns, causing oxidative stress that stimulates the inflammatory cascade, inducing the production of tumor-initiating stem cell-like cells, and activating hematopoietic stem cells and immunosuppression[16,17]. Additionally, Asian-Americans had markedly lower ALD-related mortality rates from 2007 to 2016 than non-Hispanic whites[18]. Thus, ALD poses a significant disease burden worldwide.

A current challenge in China is the lack of urgent awareness of ALD and NAFLD in society as well as by health authorities and policy makers, which has been made worse by the lack of public and private research funding. Public ALD education and engagement in addition to research advances in the field, are required to reduce the ALD burden.

This review summarizes the current knowledge regarding the ALD epidemic in China as well as the present understanding of ALD occurrence and progression at the cellular and molecular levels.

EPIDEMIOLOGY OF ALD IN CHINA

Currently, only region-based ALD studies, rather than nation-wide surveys, have been conducted in China, although some have been relatively largescale[9,19-25]. The percentage of regular alcohol drinkers among the general adult population in different areas increased from 27.0% in 2000 to 66.2% in 2015 (Table 1), and the percentage of heavy drinkers increased from 0.21% in 1982 to 14.8% in 2000, a 70-fold

increase in < 20 years. The 2.27% ALD prevalence in 2000 was increased to 8.74% in 2015. There is a notable parallel between the increased male drinking population and the increased ALD prevalence in males.

The frequencies of different ALD stages differ significantly between the general Chinese population and heavy Chinese drinkers: 0.94%-3.74% (general population) *vs* 50% (heavy drinkers) with alcoholic fatty liver, 0.42%-2.18% *vs* 10% with alcoholic hepatitis (AH), and 0.11%-0.68% *vs* 10% with alcoholic cirrhosis[9,19-23] (Table 2). Respective annual ALD frequencies of 2.7%, 2.9%, 3.0%, 3.6%, and 4.4% for 2000 to 2004 were reported by a multi-center study, revealing a steady increase in ALD[19,22]. Another two studies reported that among a cohort of 902 ALD patients, 11.2% had mild ALD, 22.6% had alcoholic fatty liver, 28.8% had AH, and 37.4% had alcoholic cirrhosis[26,27]. A hospitalization summary report (HSR) showed that viral hepatitis-related cirrhosis hospitalization declined by 10% and alcoholic cirrhosis-related hospital stay was increased by 33% after categorizing approximately 2.3 million hospitalized patients in 31 Grade 3A hospitals in Beijing between 2006 and 2010. Male patients accounted for 98% of ALD cases and 71% of viral hepatitis cases, respectively[28]. Similarly, the percentage of hospitalized ALD patients among all those hospitalized for liver diseases increased from 1.7% in 2002 to 4.6% in 2013, and the annual incidence of severe alcoholic hepatitis (SAH) increased by 2.43 times from 2002 to 2013, as reported by the 302 Hospital in Beijing[10].

In addition, the number of deaths caused by cirrhosis due to alcohol use among all ages and the age-standardized death rate per 100000 people in China were 41792 (95%UI: 36399-46769) and 5.23 (95%UI: 4.59-5.82) in 1990, compared with 41163 (95%UI: 34830-46935) and 2.89 (95%UI: 2.47-3.27) in 2013, respectively[14]. Moreover, the number of deaths caused by alcohol use disorders among all ages and the age-standardized death rate per 100000 people in China were 16488 (95%UI: 12374-27257) and 1.69 (95%UI: 1.28-2.77) in 1990, compared with 15459 (95%UI: 10132-22104) and 0.97 (95%UI: 0.64-1.39) in 2013, respectively[14].

RISK FACTORS FOR ALD IN CHINA

Several factors are known to affect ALD occurrence and progression in the Caucasian population. However, these known factors vary with geographic, racial, and developmental variations. Despite the lack of nationwide epidemiological surveys of ALD risk factors conducted in China, alcohol drinking history and total alcohol volume (concentration multiplied by drink volume) are two direct risk factors for ALD[29], in addition to the contributing factors of genetic background, age, gender, obesity/metabolic syndrome concomitant with HBV or hepatitis C virus (HCV) infection or other liver diseases, and lifestyle factors like smoking[30].

Age

In a cross-sectional survey from Shandong province, the ALD incidence increased with age until 50 years, and most ALD patients were 40-49 years old[9]. The 2017 Annals of Chinese Health and Family Planning showed the constituent ratio of ALD patients aged between 15 to 44 years old who were discharged from hospitals, and the percentages significantly increased from 20% among 45-59 year olds to 48.8% among 60 year olds and 31.2% among those > 60 years old.

In addition, a meta-analysis of adolescents found that the percentages of drinkers were highest among vocational high school students (44.7% for males, 28.8% for females). Alcohol consumption rates in high school students were higher (36.5% for males, 21.2% for females) than those in middle school students (23.6% for males and 15.3% for females). The percentages of drinkers among males were significantly higher in all three types of schools compared with those among females[31]. Although prevalence estimates among Chinese students were generally lower than those reported in Western countries, an increasing trend has been observed in recent decades[32].

Excessive alcohol consumption, especially of distilled alcoholic beverages containing high levels of alcohol (spirit or liquor), usually occurs in circumstances of formal social activities. In anticipation of establishing, maintaining, and/or developing personal or social networking relationships, peer pressure to consume an excessive amount of alcohol exists among participants in social events, such as dinners or banquets among middle-aged business clients or partners. Middle-aged people represent the main population involved in these social activities. Moreover, as they are more likely to have a relatively stable family income and independent financial status, middle-aged people in China have more accessibility to alcoholic beverages.

Table 1 population-based surveys of alcohol consumption in China

Author	Year	Area	*n*	Age (yr)	Habitual drinking (%)	Excessive drinking (%)
Li *et al*[19]	2000	Zhengjiang	18237 (M 66.0%)	38.3±12.3	27.0 (M -, F -)	14.8
Lu *et al*[20]	2000	Xi'an	3613 (M 60.6%)	36.0±13.0	35.2 (M 52.2, F 8.9)	-
Huang *et al*[21]	2005	Hu'nan	18828 (M 69.2%)	42.1±13.4	37.8 (M -, F -)	-
Chen *et al*[22]	2007	Liaoning	6598 (M 62.2%)	39.3±11.1	27.0 (M 38.3, F 5.6)	-
Wang *et al*[9]	2011	Shandong	7295 (M 48.2%)	44.7±13.9	42.76 (M 74.5, F 11.3)	-
Yan *et al*[23]	2015	Shanxi, Gansu, Xinjiang	2300 (M 75.0%)	38.1±13.3	66.2 (M 77.9, F 31.2)	-
Guo *et al*[24]	2016	Guizhou	9280 (M 47.9%)	42.7±25.5	32.1 (M 52.8, F 13.2)	-
Chang *et al*[25]	2016	Tianjin	3137 (M 45.1%)	-	32.2 (M 55.9, F 12.6)	-

Excessive drinking: alcohol consumption ≥ 40 g/d for over 5 years. M: Male; F: Female; "-": Unavailable.

Gender

In China, the proportion of males who report high alcohol consumption is higher than that of females. Chinese males typically have more social opportunities to drink than females, and a common opinion in these settings is that males who have the ability to drink large volumes are perceived as masculine. In contrast, the traditional responsibility of Chinese adult females is to manage the daily life of their families, which keeps women in these roles busy caring for children and elderly relatives. They do not have as many opportunities to participate in social engagements as males do. Thus, the delegation of family responsibility restricts the females from frequently consuming alcohol. However, as more women are pursuing professional careers, more adult women are maintaining bachelorette status, and drinking among women is no longer viewed as exceptional by Chinese society. A continued increase in the percentage of female drinkers is expected over time. According to the Global status report on alcohol and health 2018, in absolute numbers there were about 91000 more women who drank alcohol in 2016 than in 2000 despite a 5% decrease in the current worldwide drinking prevalence from 37.3% to 32.3%[7]. The prevalence rates of current drinking among women in the World Health Organization Western Pacific Region were 39.3%, 36.4%, 42.0%, and 40.7% in 2000, 2005, 2010, and 2016, respectively. In China specifically, the total, including recorded and unrecorded, per capita alcohol consumption for women was 2.2 (95%CI: 1.9-2.5) and 2.5 (95%CI: 2.4-2.6) in 2014 and 2018, respectively[7,33]. However, the age-standardized death rates for liver cirrhosis in females were 5.8 and 8.3 per 100000 population (15+) in 2012 and 2016, while the alcohol-attributable fractions were 59.8% and 41.6% in 2012 and 2016, respectively[7,33]. Women are known to express lower levels of alcohol dehydrogenase (ADH) in hepatocytes and to have different ratios of total body water and fat compared with men. Thus, compared with men, they are less tolerable of alcohol, tend to develop ALD after exposure to lower amounts of alcohol, and are more vulnerable to ALD progression[34].

Types of alcoholic beverages ingested

In China, spirits make up about 70% of the alcoholic beverages consumed, and it is estimated that up to 25% of the consumed alcohol is not registered[35]. Homemade wines including rice wines, which are not subject to taxation, are distilled by farmers in their family workshops. A cross-sectional survey[36] found that the three most commonly consumed alcoholic beverages in rural regions in Hunan province were homemade alcoholic beverages, beer, and high-alcohol liquors. In Henan, they were beer, high and low alcohol liquors. Traditional distilled spirits (*bai jiu*) are the most popular unrecorded alcohols, and the production volume is often underestimated by official statistics. It is of importance to include home brews in the drinking surveys in both China and other countries[36,37]. The main concern regarding homemade alcoholic beverages is the easy access to high alcohol drinking at an exceedingly affordable price. Furthermore, Newman *et al*[35] commented that the major health risks posed by unrecorded Chinese *bai jiu* include not only the high concentration of alcohol but also the presence of toxic impurities including heavy metals and acetaldehyde.

Genetics and ALD pathogenesis

Although the pathogenesis of ALD is complex and remains unclear, the oxidative metabolites of alcohol, including acetaldehyde and ROS, are the main culprits for ALD. Acetaldehyde is reactive with DNA and proteins and may form adducts, which act as neoantigens that elicit an immune response and contribute to liver injury.

Table 2 population-based surveys of alcoholic liver disease in China

Author	Year	*n*	Morbidity rate of ALD (%)	ALD			
				MALD (%)	AFL (%)	AH (%)	AC (%)
Li *et al*[19]	2000	18237	4.34 (M 6.36, F 0.36)	1.21	0.94	1.51	0.68
Lu *et al*[20]	2000	3613	2.27 (only one female)	-	2.16	-	0.11
Huang *et al*[21]	2005	18828	4.36 (M 6.00, F 0.52)	1.21	0.97	1.50	0.68
Chen *et al*[22]	2007	6598	6.82 (M 9.75, F 2.00)	4.29	4.29	2.18	0.35
Wang *et al*[9]	2011	7295	8.55 (M 15.76, F 1.42)	6.23	1.71	0.42	0.17
Yan *et al*[23]	2015	2300	8.74 (M 10.08, F 4.70)	4.22	3.74	0.48	0.30

ALD: Alcoholic liver disease; MALD: Mild ALD; AH: Alcoholic hepatitis; AC: Alcoholic cirrhosis; "-": Unavailable.

Acetaldehyde also interferes with DNA synthesis, methylation, and repair, facilitating HCC susceptibility.

There are two major enzyme systems that metabolize EtOH into acetaldehyde (AA) *via* oxidative degradation. Members of the ADH family in hepatocytes are the enzymes responsible for metabolizing ingested alcohol. ADH activity determines alcohol tolerance and ALD susceptibility. Mutations in *ADH* genes have been linked to both protection from and susceptibility to ALD. As examples, due to slower oxidation rates, the *ADH2*1*, *ADH3*2*, and *ALDH2*2* alleles are associated with high blood acetaldehyde concentrations, which correspond to a greater risk of adverse effects, and thus, may serve to reduce alcohol consumption and the risk of related diseases. By contrast, certain genetic variants involving *ADH2*2, ADH3*1, ALDH2*1*, and *CYP2E1*1* allow a higher oxidation rate, which corresponds to an increased alcohol clearance rate, facilitating the consumption of more alcohol and increasing the risk of alcohol-related diseases[38-40]. Clearly, ADH activity is affected by genetic polymorphisms of the *ADH* genes. Several studies from Taiwan and mainland China identified genetic polymorphisms in *ADH2, ADH3*, and *ALDH2* genes among the Chinese Han population, and they are different from those reported in the Caucasian population. Such variation in *ADH* genes may lead to differences in the susceptibilities to ALD between the Chinese Han population and Caucasians[41-43]. Our previous research showed that ALDH2 deficiency is accompanied by higher levels of serum acetaldehyde and corticosterone after alcohol consumption, leading to the attenuation of T-cell activation and concanavalin A-induced T-cell hepatitis in both mice and humans[40]. ALDH2-deficient individuals may have an elevated risk for alcohol-related cancers and diseases due to T-cell suppression[40]. We investigated *ALDH2* polymorphisms in two cohorts, one consisting of 450 alcoholic cirrhosis patients and the other consisting of 683 patients with HBV-related liver diseases, and found that the occurrence of HBV-related cirrhosis and HCC among alcohol drinkers with HBV infection was linked to polymorphism of the *ALDH2*1/*2* genes, which was also a risk factor for progression of cirrhosis to HCC and of HCC stage B to stage C or D. Less than 5% of patients with alcoholic cirrhosis were found to have the *ALDH2*1/*2* genotype, and none had the *ALDH2*2/*2* genotype. In addition, polymorphism in the PsaI/Psat restriction site of the *CYP2E1* gene was also linked to ALD susceptibility[44]. Finally, polymorphism in the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) gene may predispose ALD patients to more severe alcohol-related liver injury[45]. Recently, a large case-control multicenter study conducted in China showed that both the allele and genotype frequencies of rs738409 in the *PNPLA3* gene were significantly associated with ALD ($P = 6.25 \times 10^{-14}$ and $P = 9.05 \times 10^{-13}$)[46]. In addition, a polymorphism in the silent mating type information regulation 2 homolog 1 (*SIRT1*) gene was associated with alcoholic fatty liver disease (AFLD) in the Han population[47].

On the other hand, chronic alcohol consumption up-regulates cytochrome P450 2E1 (*CYP2E1*) gene expression in response to the need to convert alcohol to acetaldehyde. This CYP2E1-dependent microsomal ethanol oxidizing system (MEOS) generates more ROS[48]. Hepatocytes injured after alcohol intake release endogenous DAMPs. DAMPs can activate Toll-like receptor 4 (TLR4) on Kupffer cells to promote the secretion of proinflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) and to activate the inflammasome[49]. The activated Kupffer cells also secrete CXC chemokines to attract infiltrating neutrophils and other mononuclear cells, which may aggravate hepatic necroinflammation[50].

Socioeconomic status

Factors of socioeconomic status, including education, marital status, occupation, and family income, have also been linked to ALD. Individuals with a low level of education, a lack of immediate family, a high-stress job, or a low income are more susceptible to alcoholism, and the incidence of ALD is higher in these groups. Such a linkage was also reported by studies in the United States[9,51]. Single individuals tend to be financially better off, participate in more social engagements, and have more opportunities for drinking compared with married persons. Also, individuals who perform hard manual labor daily in rural areas tend to consume more alcohol, often at pubs after work[9].

Body mass index and obesity

Adipose tissue, which is an important source of proinflammatory cytokines (such as TNF-α), may facilitate ALD development and progression[52]. Both elevated BMI and visceral fat accumulation are independent risk factors for alcoholic hepatitis in ALD[53]. A study showed that the BMI was significantly higher in an ALD group than in a non-ALD group[54]. Additionally, chronic heavy alcohol consumption, obesity, and viral infections share the same steatosis pathology[55]. Data from the China Health and Nutrition Survey collected in 1997, 2000, 2004, 2006, 2009, and 2011 showed an increasing trend in the BMI of Chinese adults, with that of males increasing by 0.21 kg/m^2 per year and that of women increasing by 0.16 kg/m^2 per year[56].

HBV or HCV infection

A combination of excessive alcohol consumption and endemic chronic HBV/HCV infection may promote advancement of chronic liver diseases, regardless of the initial etiology, and increase the ALD and chronic HBV infection (CHB) burden in China[57]. Alcohol consumption by chronic HBV- or chronic HCV-infected patients is an additional risk factor for accelerated progression of chronic hepatitis to liver cirrhosis, HCC, or liver-related mortality[57,58]. Moreover, alcohol consumption may thus enable HCV evasion from the immune response and facilitate HCV replication[57]. Further studies should be directed at exploring the impact of ALD on the long-term outcomes of antiviral therapy.

A population-based study of Asian patients with chronic liver disease in the United States from 2007 to 2016 found that chronic HBV infection in different Asian populations ranged from 9%-25% in contrast to 0.5% in the general United States population[18]. A nationwide serologic survey of HBV infection in China showed that HBV surface antigen (HBsAg) positivity rates in individuals aged 1-4, 5-14, and 15-29 years were 0.3%, 0.9%, and 4.4%, respectively, in 2014, and these percentages were far lower than the average of 9.8% in 1992 due to the introduction of universal HBV vaccination[59]. The prevalence of ten HBV genotypes (A-J) varies among different parts of the world: genotypes A and D are the most prevalent in Africa and Europe, and genotypes B and C are dominant in Asia and Oceania[60,61]. In addition, age-standardized HCV-related mortality was lower in the all United States Asian population throughout the study period[18]. However, 70% of HCV-infected patients in the European and North American countries were heavy alcohol drinkers, and 30%-40% of ALD cases had concomitant chronic HCV infection. These two concurrent diseases may exert synergistic effects on hepatic necroinflammation, tumorigenesis, and oxidative stress[62]. The fact that hepatitis C-related chronic liver disease is expected to decline over time highlights the need to improve the treatment of ALD, which may soon rank as the number one cause of cirrhosis as the frequencies of ALD cases continue to rise in European and North American countries[63]. HCV infection in China has showed a steady decrease from an average 3.2% in 1992 to 0.36% in 2010[64]. HCV genotypes 1b and 2a are predominant in China, whereas HCV genotypes 1 and 3 account for most HCV infections in Europe[65].

MANAGEMENT OF ALD IN CHINA

As a result of rapid urbanization, improved living standards, and reductions in physical activity, ALD is emerging as a new public health problem in China. However, health authorities, healthcare providers, and the general population lack an urgent awareness of the effects of ALD. Therefore, both public education and an ALD awareness campaign that target the general population as well as physicians are urgently required in China. The Chinese Association for Study of Liver Diseases established the fatty liver and ALD subsections in 2001 and has published and updated several editions of the Clinical Practice Guidelines for Diagnosis and Management of ALD since 2003, with the latest updates published in 2018[66].

Abstinence from alcohol and nutritional support

Abstinence from alcohol is the most effective approach to mitigating or ceasing alcohol-related liver injury. International guidelines from China, the United States, and Europe, as well as questionnaires including the Alcohol Use Disorders Identification Test (AUDIT), the Michigan Alcoholism Screening Test (MAST), and the CAGE alcohol screening questionnaire, emphasize the discrimination of alcohol dependence or abuse[66-68]. Moreover, despite progress in drug-based ALD treatments, ALD therapeutics remain insufficient[69]. Currently, only a few drugs are approved for ALD treatment, including acamprosate, disulfiram, naltrexone, and nalmefene, and not all of them are available in every country[63]. A main focus of clinical research is rectifying alcohol use disorder (AUD) in ALD patients. Currently, a combination of drug therapy, psychosocial interventions, and medical management is recommended. Nonpharmacological treatment consists of cognitive behavioral therapy, outpatient motivational consultation, and attendance at Alcoholics Anonymous meetings. If patients develop psychological problems, fail to improve with outpatient therapy, and live in an unstable family, in-patient therapy is highly advised. Drug-based therapy for AUD is also available. Attention should focus on the prevention of withdrawal syndrome during abstinence. In addition, sufficient nutritional supplementation of vitamin B, C, D, E, and K, and folate should be provided to ALD patients[70]. Vitamin D deficiency was suggested to promote liver fibrosis and/or inflammation, particularly during chronic HCV infection[71]. A high-protein and low-fat diet is suggested for patients with alcoholic cirrhosis. A suggested energy supply of 35-40 kcal/kg body weight (BW) per day (147-168 kJ/kg BW per day) and a protein intake of 1.2-1.5 g/kg BW per day are recommended by the European Society for Clinical Nutrition and Metabolism guidelines[72].

Drug therapy

Although abstinence is advised, not all patients can maintain sobriety. Thus, some patients may require drug-based treatment. Treatment with corticosteroids (CS) may increase the survival rate of patients with SAH. However, patients who have a Lille score of ≥ 0.45 may not benefit from continued administration of CS. The antioxidants metadoxine and N-acetylcysteine (NAC) have also been suggested for treatment of ALD. Metadoxine accelerates the clearance of alcohol from the serum and improves alcoholic symptoms and abnormal behavior[73]. NAC replenishes the glutathione level in hepatocytes, reduces free radicals, and inhibits the expression of nuclear factor κB and TNF-α. NAC can also prevent alcohol addiction and reduce alcohol consumption[74]. Additional drugs can be used to treat ALD, including S-adenosyl-L-methionine (SAMe), polyene phosphatidylcholine, glycyrrhizic acid products, silymarin, polyene phosphatidylcholine, reduced glutathione, and bicyclol therapy. SAMe, a precursor of glutathione and a major methyl donor for methyltransferase reactions, was shown to improve the symptoms and biochemical parameters of ALD[75]. Polyene phosphatidylcholine can prevent histological aggravation in ALD patients[76]. The glycyrrhizic acid products silymarin, polyene phosphatidylcholine, and reduced glutathione share antioxidation and anti-inflammation effects and to some extent protect cellular membranes and organelles, improving liver biochemical indices[77]. Bicyclol therapy can also alleviate the ALD symptoms[78].

Many ALD patients in China, especially those who fail to respond to treatment with small molecule drugs, pursue traditional Chinese medicine (TCM) as an adjunct or alternative therapy. Several TCM formulae are known to be effective at mitigating hepatic fibrosis. Several herbal medicines, including *Cnidium monnieri* (*L.*) Cusson (Apiaceae), and *Curcuma longa L.* (Zingiberaceae), have been used for ALD treatment in China[79]. Gao *et al*[80] suggested that ginsenoside Rg1 is a potential hepatoprotective agent that functions through glucocorticoid receptor (GR) and the GR-related nuclear factor-κB pathway. Wu *et al*[81] suggested that a TCM formula of Qinggan Huoxue can effectively alleviate the ALD pathology in rats through the lipopolysaccharide-Kupffer cell signaling pathway. Because TCM formulae consist of multiple components with complex chemistry and pharmacology characteristics, they could be made more effective once the active components and their underlying mechanisms are clearly elucidated. The potential side effects of TCM must be evaluated through large-sample, randomized, double-blind clinical trials that are consistent with the principles of evidence-based medicine.

For ALD patients who cannot tolerate steroid drugs, new therapies are being evaluated in clinical trials, including therapies based on human induced pluripotent stem cells, bovine colostrum and hyperimmune bovine colostrum (ClinicalTrials.gov NCT02265328; NCT02473341; NCT01968382), fecal microbiota transplantation (ClinicalTrials.gov NCT03091010; NCT02458079), and granulocytapheresis.

Liver transplantation (LT)

LT is a curative therapy for patients with severe alcoholic liver cirrhosis. The

indications for LT in China include HBV-related HCC; HBV-, HCV-, or alcohol-related cirrhosis; and biliary atresia in children. The 2011 edition of the China Liver Transplant Annual Scientific Report prepared by the China Liver Transplant Registry (CLTR) reported 561 cases of LT for ALD, which accounted for 2.77% of all LT cases. The number of patients with end-stage ALD who have received LT in recent years in mainland China has been increasing[82]. Before orthotopic LT, a 3-6-mo period of alcohol abstinence is required as outlined by the 2018 Guidelines for Management of Alcoholic Liver Disease, whereas a similar requirement has been removed from the ACG Clinical Guidelines and EASL Clinical Practical Guidelines[66-68]. A recent retrospective analysis of 147 patients who underwent early LT (without 6 mo of abstinence) for SAH reported a 1-year survival rate of 94% and 3-year survival rate of 84%, and sustained alcohol use after LT was infrequent but associated with increased mortality, as reported by the American Consortium of Early Liver Transplantation for AH[83]. A retrospective analysis of 17 Chinese ALD patients who received LT found that survival rates at 25, 50, and 100 wk after LT were 94.1% (16/17), 82.4% (14/17), and 64.7% (11/17), respectively[84]. Another follow-up study of 40 LT patients from April 2005 to June 2017 showed that the 1-year survival rate was 81.0% and the 5-year survival rate was 77.0%, and these rates were comparable to outcomes reported in other countries[85]. However, the mortality of SAH remains high, because the shortage of donor organs and high cost of surgery limit patients' access to LT[86].

Regulation of alcohol consumption

Alcohol consumption is impacted by alcohol and taxation policies as well as social and cultural norms. In China, the alcohol taxes were increased in 2002, and the alcohol sale restrictions and the license requirement were implemented in 2004. In 2007, the laws that punish drunk drivers began to be enforced, and restrictions on alcohol advertisements took effect in 2010[87]. However, the alcohol policy in China is weaker than those in its neighboring countries in many aspects, which favors alcohol consumption, leading to consequent alcohol-related problems. There are no minimal legal age requirements for purchasing or selling alcoholic beverages, no restrictions on home-made alcohol beverages, no enforceable regulations on alcohol sponsorship/sale promotion, and no legal requirements for warning labels on alcohol advertisements/containers in China[7,87]. We advocate a strong and sensible alcohol policy that effectively regulates alcohol production quality and consumption to reduce the occurrence of ALD in China[88].

DISCUSSION

Given the continually increasing ALD incidence and the severity of the ALD outcomes, an effective management strategy that includes effective prevention and treatment of ALD is required. Chief among the components of ALD management are abstinence, mitigation of alcohol withdrawal symptoms, nutritional support, and management of cirrhosis-related complications. A major challenge in SAH management is that most therapeutics have been found to only extend short-term survival, not long-term survival, in most trials. Abstinence, nutrition, and the underlying cirrhosis and its complications are the main factors found to impact 6-mo survival. The outcomes tend to be poor in SAH patients who show no therapeutic response. New SAH therapeutics may not be available for long time since they remain in the developmental stage. Early LT for highly selected patients requires extensive evaluation[89]. LT offers the best outcomes for patients with alcoholic cirrhosis if they completely abstain from alcohol. The number of patients with end-stage ALD who have undergone LT in mainland China has been steadily increasing over the last 10 years. In addition to drugs and procedures, ALD patients may require care and mental support from doctors, family members, and society to gradually regain confidence and resilience to avoid relapse.

In addition, government action is required through public education, regulation of alcohol production and consumption, research funding, and tax policy. Family or farm-based alcohol production in China is not subject to sufficient oversight, and the legal requirements for alcohol sale and consumption have yet to be established. A public health-oriented commission or agency could be established to oversee the alcohol market and to propose national alcohol-related legislation to discourage excessive alcohol drinking, especially in the young generation[90]. Then it is important to enforce the licensing requirements for alcohol production and alcohol quality standards, and gradually prevent low-quality alcoholic beverages from reaching the market. All alcohol containers are required to clearly display a warning label[91]. The regulations on alcohol advertisement should include regulating sponsorship and

promotion, and restrictions may need to be applied to online sales and other eCommerce forms, which may shield minors from exposure to alcohol advertisements. The laws to detect and prohibit drunk driving and to stipulate punishments for violators should be strengthened, including random breath testing of serum alcohol concentration, sobriety checkpoints, mandatory treatment, and other penalties[92]. A high alcohol tax may deter some people from drinking excessively. A legal minimum age for the purchase and consumption of alcohol may delay drinking among minors. A sustained public understanding and awareness of the hazardous effects of excessive alcohol drinking should be established in the general population as well as in the beverage and healthcare industries in China. An alcohol-related health course could be included in the school curriculum and professional training[93].

CONCLUSION

The number of ALD patients and incidence of ALD among chronic liver diseases in China will continue to increase in the foreseeable future. The pathogenesis of ALD in the Chinese population may be unique in some aspects relative to the well-characterized ALD pathogenesis in Western countries, considering notable differences in drinking patterns, composition of food, population genetics, alcohol metabolism, and behaviors between the different populations. Thus, the study of ALD in the Chinese population has been insufficient and should continue to expand, including updating of the clinical ALD diagnosis criteria; metabolic, clinical, and histologic features; and outcomes. Of course, the management on alcohol addiction and alcohol withdrawal should also be improved. Development and evaluation of non-invasive test procedures and identification of simple and accurate biomarkers for early diagnosis and prognosis estimation should be a priority. Importantly, we must discover and develop new, safer, and more effective ALD drugs, as well as a reliable and accurate recurrence prediction model. Consensus indicators for the selection of ALD patients for LT need to be established in China.

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