CMH

Review

KASL Clinical Practice Guidelines:
Management of Alcoholic Liver Disease

The Korean Association for the Study of the Liver (KASL)[*]

PREAMBLE

Aims

In Korea, alcoholic liver disease (ALD) is the second most common cause of chronic liver disease after viral liver disease, and the rate of alcohol-related deaths is high, at 9.6 deaths per 100,000 persons per year. Nevertheless, the Korean culture is lenient toward drinking and the inebriated state, which is due to alcohol being considered an important social lubricant for both business and private gatherings. ALD tends to be thought of as a personal problem, and as such its importance is underestimated. Furthermore, academic interest in ADL is dwindling since the advent of antiviral therapy. However, given the keen worldwide interest and research into ALD, there remains a need for clinical practice guidelines that are tailored to the Korean healthcare system for the management of this disease. This need prompted the Korean Association for the Study of the Liver (KASL) to develop the "KASL Clinical Practice Guidelines: Management of Alcoholic Liver Dis-

ease", based on a systematic approach to reflect evidence-based medicine and expert opinion in internal medicine and psychiatry, with the aim of setting clinical practice guidelines for the management of ALD and improving public health in Korea.

Target population, healthcare system, and intended users

The main targets of these guidelines are patients in the Korean healthcare system with ALD or alcohol use disorder. The guidelines are intended to provide useful information and guidance to physicians, caregivers, and healthcare workers with regard to ALD diagnosis, education, and research.

Systematic review of the literature, level of evidence, and grade of recommendation

The guidelines were developed based on recent studies and evidence, with key questions for each section formulated based on

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[*]Clinical Practice Guidelines Committee of KASL for the Management of Alcoholic Liver Disease:
Dong Joon Kim (Committee Chair, Hallym University College of Medicine), Young Seok Kim (Soonchunhyang University College of Medicine), Jeong Ill Suh (Dongguk University College of Medicine), Yoon Jun Kim (Seoul National University College of Medicine), Jae Young Jang (Soonchunhyang University College of Medicine), Tae Yeob Kim (Hanyang University College of Medicine), Ki Tae Suk (Hallym University College of Medicine), Byung Seok Lee (Chungnam National University School of Medicine), Hyung Joon Kim (Chung Ang University College of Medicine), Seung Ha Park (Inje University College of Medicine), Won Hyeok Choe (Konkuk University Medical School), In Hee Kim (Chonbuk National University Medical School), Hyun Ju Min (Gyeongsang National University School of Medicine), Chang Hyeong Lee (Catholic University of Daegu School of Medicine), Hyung Joon Yim (Korea University College of Medicine), Soo Young Park (Kyungpook National University School of Medicine), Sang Kyu Lee (Hallym University College of Medicine, Department of Psychiatry), Jeong Seok Seo (Konkuk University Medical School, Department of Psychiatry)

the PICO (Patient/Problem, Intervention, Comparison, Outcome) format. Using these key questions, a literature search was performed using MeSH terms or keywords in PubMed/MEDLINE, KoreaMed, and Korean Medical Database to collect and analyze relevant studies. Studies from the past 5 years were preferentially selected and the quality of evidence was evaluated with the aid of a categorized checklist. The decision to include or exclude a study was based on standards set by the committee.

The level of evidence and grade of recommendation were stratified according to the modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (Table 1).[1] "Level of evidence" refers to the level of confidence in the estimate of the effect, based on consideration of the study design and quality, and the amount, consistency, and directness of evidence. "Grade of recommendation" refers to the level of confidence associated with a recommendation, based on consideration of the quality of evidence, the balance between the desirable and undesirable effects of an intervention, the preferences, and the cost.

These guidelines were developed based on evidence-based medicine and expert opinion. However, the recommendations presented here should not be taken as inflexible standards of care that should be followed without exception. Different opinions may exist regarding the best treatment option for an individual patient.

List of key questions

The committee identified the following key questions to be covered in these guidelines. Current evidence and recommendations are provided for each key question.

1. What is the burden of ALD in Korea?
2. How should moderate drinking, heavy drinking, binge drinking, hazardous drinking, harmful drinking, and alcohol use disorder be defined?
3. What diseases are included in the spectrum of ALD?
4. What is the natural history of ALD?
5. How do the quantity of alcohol consumed, drinking habit, and type of alcohol affect the development of ALD?
6. How do sex, ethnicity, and obesity affect ALD?
7. What is the relationship between viral hepatitis and ALD?
8. What are the characteristics of the pathophysiology of ALD?
9. What are the criteria for the clinical diagnosis of ALD?
10. Is a liver biopsy necessary for the diagnosis of ALD?
11. What is the prognosis for alcoholic hepatitis?
12. What are useful prognostic factors for alcoholic hepatitis?
13. How is therapy for alcohol withdrawal syndrome (AWS) implemented?
14. What methods are available to promote alcohol abstinence?
15. Is enteral or parenteral nutritional support helpful for patients with ALD?
16. What treatments increase the survival rate in alcoholic hepatitis?
17. Which patients should be given steroids or pentoxifylline treatment?
18. How should treatment outcomes for alcoholic hepatitis be evaluated?
19. What should be done for patients with alcoholic hepatitis who are nonresponsive to medical treatment?
20. What are the indications for liver transplantation in patients with ALD?
21. What pharmacologic agents are being tried for treatment of ALD?
22. What policies are needed to decrease harmful use of alcohol in Korea?

Table 1. The grading of recommendations, assessment, development, and evaluation (GRADE) system

Evidence quality	Description	
High	Further research is very unlikely to change our confidence in the estimate of the effect	A
Moderate	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change this estimate	B
Low	Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate. Any change of estimate is uncertain	C
Recommendation strength	**Description**	
Strong	Factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes, and cost	1
Weak	Variability in preference and values, or greater uncertainty. The recommendation is made with less certainty, higher cost or resource consumption	2

Endorsement, release, and plan for updates

These guidelines were reviewed by an external review board comprising 12 ALD specialists who are members of the KASL, and 1 specialist in guidelines methodology. The final manuscript was endorsed by the board of executives of the KASL.

All of the required funding was provided by the KASL. These guidelines may not be altered, modified, or distributed without the permission of the KASL.

The Korean version of the KASL Clinical Practice Guidelines for the Management of Alcoholic Liver Disease was released in July 2013 on the KASL website at http://www.kasl.org. Updates are planned when new reliable evidence is accumulated. Detailed plans for updates and revision will be posted on the KASL website.

EPIDEMIOLOGY

Alcohol consumption ranks third among the risk factors for disease and disability throughout the world, and causes 2.5 million deaths annually, constituting 4% of all deaths worldwide.[2] ALD, including liver cirrhosis and hepatocellular carcinoma (HCC), is responsible for approximately 25% of deaths due to alcohol consumption,[3] which demonstrates the importance of ALD in the general population. The number of alcohol-related deaths is directly proportional to the per-capita alcohol consumption.[4,5] According to a European study, every 1 L increase in per-capita alcohol consumption increases the incidence of liver cirrhosis by 14% in men and 8% in women.[6]

The Korean culture is lenient toward drinking and the inebriated state. Alcohol is considered a social lubricant, and drinking is thought to be an important component in business and various other social interactions. Alcohol consumption has increased over the past 40 years in Korea concomitantly with the country's rapid socioeconomic development. The per-capita alcohol consumption in Korea increased from 7 L in the 1980s to 15 L during 2003-2005, and is now considered to be among the highest in the world (Fig. 1).[3] Economic loss due to alcohol has increased in line with the increase in alcohol consumption, from 2.6% of the gross domestic product (GDP) in 2000 to 2.9% of the GDP in 2004.[7,8] The large absolute increase in alcohol consumption has led to a rapid increase in alcohol-related diseases and accidents.[9] According to recent data from the Korea National Health and Nutrition Examination Survey (KNHANES), the prevalence of alcohol use disorder, identified as a score of 12 or higher on the Korean version of the Alcohol Use Disorders Identification Test (AUDIT, AUDIT-K), increased from 21.3% in 2005 to 25.1% in 2009, which
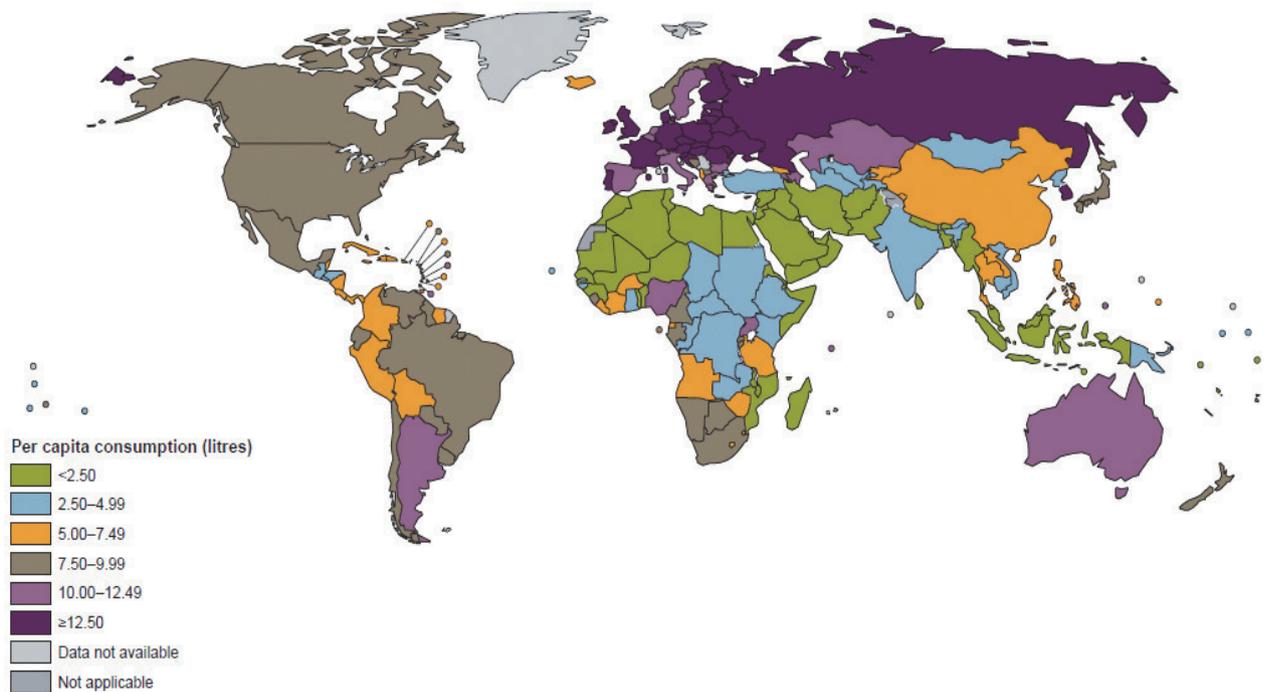

Figure 1. Adult alcohol consumption per capita in 2005 (World Health Organization Global Status Report on Alcohol and Health, 2011).

represents an increase of approximately 4%. About 7% of Koreans had an AUDIT-K score of 20 or higher, a level at which tests for alcohol dependence would be necessary.[10,11]

As patients with asymptomatic ALD tend not to visit medical facilities, only a limited number of studies of the incidence and prevalence of ALD are available. According to a study from the USA, the incidence of chronic liver disease was 72.3 per 100,000, among which 24% had chronic liver disease due to alcohol.[12] Although there have been no official reports regarding the prevalence of ALD and the proportion of alcohol-related causes for liver cirrhosis in Korea, studies based on inpatient data found 25-30% cases of liver cirrhosis have an alcoholic etiology.[13,14] According to recent Korean studies based on data from the 2009 KNHANES, approximately 7% of Korean adults are heavy alcohol consumers (men: >40 g/day, women: >20 g/day),[15,16] and approximately 25% of these heavy alcohol consumers exhibit abnormal liver-function test results.[16] Since most cases of ALD occur in patients with alcohol use disorder, a brief discussion thereof is presented in the following section.

[Recommendation]

1. Due to the recent increase in alcohol consumption in Korea, the epidemiology of ALD including its incidence and prevalence must be investigated. (B1)

Future research

1. There is a need for a nationwide study of the epidemiology of ALD in Korea.

HAZARDOUS DRINKING AND ALCOHOL USE DISORDER

Excessive drinking is associated with an increased risk of disease, the most prominent of which is ALD.[17-19] Therefore, it is of critical importance that hazardous drinkers are identified and treated in order to prevent or slow the progression of ALD. Hazardous drinkers are generally identified based on criteria developed by the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the World Health Organization (WHO), in which moderate drinking, heavy drinking, binge drinking, hazardous drinking (NIAAA: at-risk drinking), and harmful drinking are defined based on both the amount of alcohol consumed and drinking habit (Table 2).[20-22] Although most patients with alcohol use disorder are hazardous drinkers, hazardous drinking is generally defined as the stage before alcohol use disorder, and is therefore only used when alcohol use disorder is not present.

Alcohol use disorder is diagnosed with a focus on psychological, social, and physical problems, and disability caused by alcohol consumption in the past 12 months, rather than on the amount of alcohol consumed or the drinking habit. Criteria from the WHO and the American Psychiatric Association (APA) are generally used. The APA's Diagnostic and Statistical Manuals of Mental Disorders, 4th Edition (DSM-IV) divides alcohol use disorder into two categories: alcohol abuse and alcohol dependence.[21] Alcohol abuse, which generally refers to the stage prior to alcohol dependence, is defined as persistent drinking despite recurrent social, interpersonal, and legal problems as a result of the alcohol use, and it is known that around 10% of alcohol abusers progress to alcohol dependence.[23] Alcohol dependence is a condition that results from the prolonged and (usually) high consumption of alcohol that has resulted in physiological dependence on this consumption. This dependence produces significant problems in the person's life. Due to the ambiguity in the definition of alcohol abuse, the WHO's International Classification of Diseases, 10th Revision (ICD 10) does not classify it,[22] and alcohol use disorder is defined in the recently revised DSM-V as mild, moderate, or severe based on the severity rather than alcohol abuse versus dependence (Appendix 1).[24,25]

Screening test for alcohol use disorder

Given that a significant portion of patients who visit primary care facilities are hazardous drinkers, the risk for many diseases due to alcohol consumption may be decreased with proper recognition and interventions that lead to abstinence or decreased drinking.[26-29] The best screening test for hazardous drinkers is a questionnaire, since this has been shown to have a higher sensitivity than blood-based tests.[30]

While many questionnaires are available, the ones most frequently used are the CAGE (Cut down, Annoyed, Guilty, Eye-opener) questionnaire and the AUDIT questionnaire. The CAGE questionnaire is simple, being based on four yes/no questions, and while easily adoptable it has low sensitivity for hazardous drinking, the stage before alcohol use disorder (Appendix 2).[28,31-35]

AUDIT is a ten-item questionnaire developed by the WHO and is appropriate for most primary care settings (Appendix 3).[35,36] The first three questions measure the quantitative aspects of drinking

Table 2. Definitions of moderate drinking, heavy drinking, binge drinking, at-risk drinking, hazardous drinking, harmful drinking, alcohol abuse, and alcohol dependence[20–22]

Definitions of moderate drinking, heavy drinking, binge drinking, and at-risk drinking [National Institute on Alcohol Abuse and Alcoholism (NIAAA)]; 1 standard drink = 14 g	
Moderate drinking	Men <65 years: ≤14 standard drinks per week Men ≥65 years and all women: ≤7 standard drinks per week
Heavy drinking	Men <65 years: >14 standard drinks per week Men ≥65 years and all women: >7 standard drinks per week
Binge drinking	Men <65 years: ≥5 standard drinks within 2 hours Men ≥65 years and all women: ≥4 standard drinks within 2 hours
At-risk drinking	Heavy drinking or binge drinking
Definitions of hazardous drinking and harmful drinking [World Health Organization (WHO)]	
Hazardous drinking	A level of consumption or pattern of drinking that is likely to result in harm should the present drinking habit persist (the WHO working definition describes it as a regular average consumption of 20–40 g/day for women and 40–60 g/day for men)
Harmful drinking	A pattern of drinking that causes either physical or mental damage to health (the WHO working definition describes it as a regular average consumption of >40 g/day for women and >60 g/day for men)
Definitions of alcohol abuse and alcohol dependence (fourth edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV] of the American Psychiatric Association)	
Alcohol abuse	Alcohol abusers are those who drink despite recurrent social, interpersonal, and legal problems as a result of alcohol use
Alcohol dependence	Alcohol dependence is a condition resulting from the prolonged and usually intense consumption of alcohol that has resulted in a physiological dependence on alcohol consumption. This dependence results in significant problems in the person's life
Alcohol use disorder	Alcohol abuse or alcohol dependence

such as the quantity consumed and the drinking habit, the next three items gauge alcohol dependence, and the last four items measure the level of harmful drinking such as the psychological and social impacts. AUDIT is the most appropriate test for identifying both alcohol use disorder and hazardous drinking,[37-39] with AUDIT-K being used for a Korean cohort (Appendix 4).[40] The disadvantages of AUDIT include the larger number of questions and the longer time required to grade each question. Therefore, a shorter version has been developed, called AUDIT-Consumption (AUDIT-C), which employs only the first three questions regarding alcohol consumption. This has the advantage of a shorter testing time while maintaining a relatively high sensitivity and specificity.[41,42] Given the limited amount of time available for outpatients in Korea, the third question of AUDIT (AUDIT-3) alone can also be used to reduce the response time, since in this version of AUDIT the third question of AUDIT regarding binge drinking is asked first, and if the answer is negative for the past 1 year, screening is ended early due to the low likelihood of that patient being a hazardous drinker; while for a positive answer, additional AUDIT questions are asked to complete the screening test.[41]

[Recommendations]

2. If a patient appears to be at risk of alcohol-related medical problems, a structured questionnaire, such as AUDIT, should be administered to obtain more qualitative information about a patient's alcohol consumption and problems. (A1)

3. AUDIT-K is recommended as a screening test for outpatients with alcohol use disorder; alternatively, AUDIT-C or AUDIT-3 may be used for convenient testing. (B1)

Future research

1. There is a need to assess the prevalence of ALD in patients with alcohol use disorder.

NATURAL HISTORY OF ALCOHOLIC LIVER DISEASE

ALD encompasses a broad spectrum of diseases including fatty liver, hepatitis, liver cirrhosis, and HCC.[43] Multiple stages of liver

injury may coexist in a given individual.[44-46] In ALD, the occurrence and severity of liver fibrosis is important in the progression of the disease to liver cirrhosis (Fig. 2). A Korean study tracking 727 patients with ALD for an average period of 480 days found that the overall death rate was 14.6%, with the main causes of death being variceal bleeding (31.1%), liver failure (24.5%), and hepatorenal syndrome/sepsis (11.3%).[47] However, the natural history of ALD remains unclear. Regardless of the spectrum of ALD, abstaining from alcohol prevents progression of the disease, improves the survival rate, and decreases the need for liver transplantation.[48] Moreover, liver fibrosis and liver cirrhosis may occur in 5-15% of abstaining patients, and so abstinence per se does not guarantee a disappearance of ALD.[49-51]

Alcoholic fatty liver

Alcoholic fatty liver, also known as alcoholic steatosis, is the ini-

tial presentation of liver injury due to chronic alcohol consumption. Fatty liver is the most common disease associated with alcohol use, and is seen in 80-90% of heavy drinkers.[52] While full recovery is possible with abstinence at this stage, one study found that continued alcohol use (≥400 g/week) increased the risk of progression to cirrhosis in 30% of cases, and to fibrosis or cirrhosis in 37%.[53] However, significant liver injury may still occur in individuals who drink less. Once alcoholic fatty liver develops, it is not clear whether it will remain a fatty liver or progress to a more severe liver disease. Comorbidities due to environmental and genetic factors, viral hepatitis, obesity, and HIV infection may convert alcoholic fatty liver into steatohepatitis.

Alcoholic hepatitis

Alcoholic hepatitis (also known as alcoholic steatohepatitis), which is usually accompanied by fatty liver disease includes a
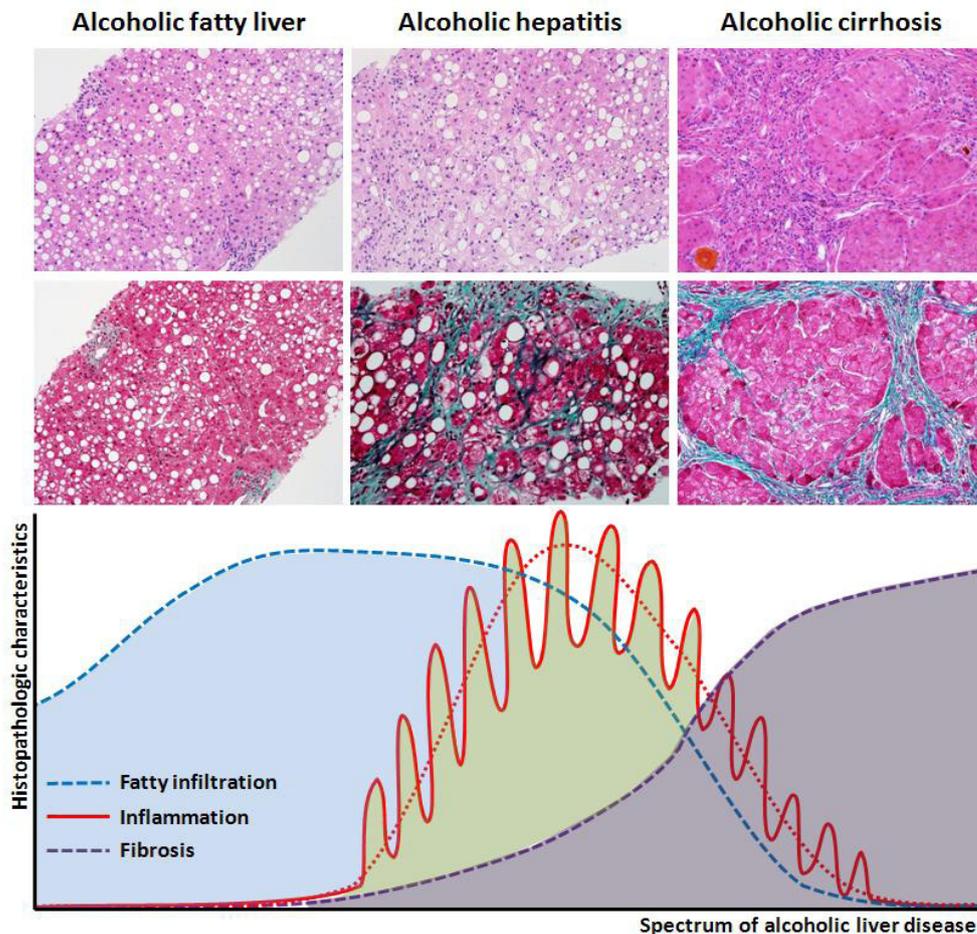

Figure 2. Natural history, spectrum, and pathophysiology of alcoholic liver disease.

broad spectrum of pathological processes. Symptomatic patients present with advanced liver disease, with concomitant cirrhosis in more than 50% of them.[54] The prognosis is even worse with severe alcoholic hepatitis, with a 1-month mortality of 40%.[55] Drink excessively, may induce recurrent episodes of alcoholic hepatitis in patients with ALD, and if this is severe or associated with liver cirrhosis, complications occur due to liver failure and portal hypertension, leading to a high short-term mortality. In addition, long-term follow-up of these patients has shown that they rarely improve, instead usually remaining with alcoholic hepatitis or progressing to liver cirrhosis.[56] Liver fibrosis is common in alcoholic hepatitis and is accelerated in the presence of chronic alcoholic hepatitis.[57] Even in patients with fatty liver or steatohepatitis but without liver fibrosis, 38-56% will eventually progress to liver cirrhosis with continued alcohol consumption.[58-61]

Alcoholic liver cirrhosis

Long-term excessive drinking results in a 15-30% lifetime risk of alcoholic liver cirrhosis.[52,53,62] At the time of diagnosis of alcoholic liver cirrhosis it is accompanied by no complications in 24% of patients, ascites alone in 55%, variceal bleeding alone in 6%, combined ascites and variceal bleeding in 4%, and hepatic encephalopathy in 11%.[63] In a patient initially presenting without complications, ascites (12%), variceal bleeding (6%), and hepatic encephalopathy (4%) may appear as a first complication within 1 year of diagnosis.[63] The rate of decompensation within 1 year of a diagnosis is 37.6% with alcoholic liver cirrhosis, compared to 25.2% in non-alcoholic liver cirrhosis.[64]

As in other diseases, alcoholic liver cirrhosis may lead to decompensated liver cirrhosis and is associated with a risk of developing HCC.[65] The incidence of HCC is 7.2-16.0% in alcoholic liver cirrhosis, with a 1% annual risk in patients with decompensated alcoholic liver cirrhosis.[61,66-69] Viral hepatitis plays a significant role in the development of HCC in chronic drinkers.[70]

The overall risk of death in patients with alcoholic liver cirrhosis is 5-30 times higher in alcoholics than in the general population.[61,71] For advanced alcoholic liver cirrhosis the median survival time is 1-2 years and the 5-year survival rate is 23-50%, which is worse than that for non-alcoholic liver cirrhosis.[72] In compensated alcoholic liver cirrhosis, the 5-year survival rate approaches 90% with abstinence but decreases to less than 70% with continued drinking.[61,73] In decompensated alcoholic liver cirrhosis the 5-year survival rate is 60% with abstinence and 30% with continued

drinking.[74] The median survival time for decompensated alcoholic liver cirrhosis is 61 months,[75] and 80% of patients who continue drinking even in the presence of ascites will die within 7 months.[76] The 1-year mortality rate is 17% among patients with liver cirrhosis but without any complications, while this increases to 20-64% if complications develop, in which case the 5-year mortality rate approaches 58-85%.[48,63]

Future research

1. There is a need to elucidate the natural history of ALD.

RISK FACTORS FOR ALCOHOLIC LIVER DISEASE

Quantity of alcohol consumed

A standard drink is sometimes used as a unit measure to estimate the quantity of alcohol consumed, and it varies markedly between countries; in Korea it corresponds to 12 g of pure alcohol. The risk of ALD substantially increases in both sexes when alcohol consumption exceeds 30 g/day.[52] An increased risk of liver injury with alcohol consumption exceeding 30 g/day was found in the large-scale Dionysos cohort study performed in northern Italy.[77,78] There are also other reports of a proportional relationship between the quantity of alcohol consumed and the risk of ALD. The minimum amount of alcohol required for liver cirrhosis is 20-40 g/day in men and 10-20 g/day in women, and most retrospective studies also show that the risk of liver injury is increased when alcohol consumption exceeds 40-80 g/day.[79-84] Many prospective studies have found a proportional relationship between the quantity of alcohol consumed and the presence of alcoholic liver injury.[50,85,86] According to the USA guidelines for non-alcoholic fatty liver disease, significant alcohol consumption has been defined in the past 2 years as exceeding 21 standard drinks per week in men and 14 standard drinks per week in women.[87,88]

In conclusion, there is a quantity dependent relationship between the amount of alcohol consumed and the risk of ALD. Although most prospective and retrospective studies demonstrate that the prevalence of liver injury increases in proportion to the daily alcohol intake, this relationship does not always hold, suggesting that other factors, such as genetic predisposition, can also be involved.[89,90]

Drinking habit

ALD is seen more frequently in daily drinkers than in intermittent drinkers.[50,78,91] Binge drinking, a form of drinking habit that has recently surfaced as a social problem in many countries, is defined as consuming more than five drinks for men and four drinks for women over a time period of 2 hours (Table 2).[83] This consumption of a large amount of alcohol over a short period of time is associated with the development of ALD.[92,93] The risk of ALD is also increased with habits such as drinking without meals, drinking at multiple locations at a time, mixing drinks, and initiating alcohol drinking at a younger age.[52,94]

Types of alcohol

While few studies have investigated the association between type of alcohol and liver injury, the available data suggest that liver injury is associated more strongly with the total quantity of alcohol consumed than with the type of alcohol. A notable finding is that small amounts of wine reportedly decrease mortality rates associated with both cardiovascular and non-cardiovascular disease, including liver disease.[95,96] However, there is still controversy regarding the association between the type of alcohol consumed and the risk of liver injury, especially for liver cirrhosis.

Sex

The frequency of liver injury is higher among women than men, even when the same quantity of alcohol is consumed. Many studies have found that the incidence of alcoholic liver injury is higher in women than in men with a daily alcohol consumption of 30-80 g.[85,97,98] Liver injury occurs more easily in women, including over shorter time periods or involving smaller quantities of alcohol.[99,100] The relatively safe level of alcohol consumption in women has been reported as less than 10-20 g.[59,81,86,97,101] In a large prospective study, the risk of developing ALD with a weekly alcohol consumption of 336-492 g differed significantly between men (7.0) and women (17.0).[97] The risk of liver cirrhosis was dramatically increased in women with a daily alcohol intake exceeding 40 g.[79,99,101] The blood alcohol concentration is higher in women than in men after consuming the same amount of alcohol, resulting in a higher risk of ALD.[102] Women exhibit a decreased level of alcohol dehydrogenase (ADH) in the stomach, resulting in a slower first step of alcohol metabolism, increased bioavailability of alcohol, and increased risk of liver injury.[98] In addition, factors such as a lower body distribution of alcohol due to a higher body fat content and an estrogen-induced increase in oxidative stress and inflammation contribute to the increased risk of ALD in women.[103]

Ethnicity

There may be an association between ethnicity and the risk of alcoholic liver injury.[104] The frequency of alcoholic liver cirrhosis is higher in African-American and Latin-American men than in white men, and the death rate for this condition is the highest among Latin-American men.[105] These differences seem to be independent of the quantity of alcohol consumed.[106]

Malnutrition

Protein-calorie malnutrition is a common clinical manifestation of ALD.[107] The degree of malnutrition is known to be strongly correlated with the development of complications such as ascites, hepatic encephalopathy, and hepatorenal syndrome, and a gradual increase in mortality.[108] ALD is accompanied by deficiencies in micronutrients such as folate, thiamine, pyridoxine, vitamin A, vitamin E, zinc, and magnesium, and such deficiencies in folate, vitamin E, and zinc may accelerate liver disease.[109,110]

Obesity

Obesity increases the severity of alcohol-induced liver injury.[111] The relationship between obesity and alcohol consumption differs between men and women.[112,113] In obese persons, excessive drinking leads to increased risks of liver disease,[114,115] liver cirrhosis, and mortality.[116-118] High body mass index and fasting glucose are independent risk factors for the progression of liver fibrosis even after correcting for the amount of alcohol consumed and the duration of alcohol abuse,[119] which is thought to be due to insulin resistance and hyperinsulinemia.[120] Therefore, obesity is an important risk factor for liver cirrhosis in the presence of excessive drinking.[119,121]

Genetic factors

Concomitant alcoholic liver cirrhosis is seen three times as frequently in monozygotic twins than in dizygotic twins, suggesting a genetic susceptibility in ALD.[89] Several family studies have also suggested an association between alcohol dependence and genetic factors.[122,123]

Genetic polymorphisms in enzymes involved in alcohol metabolism, such as ADH2, ADH3, and aldehyde dehyrogenase 2 (ALDH2), are related to alcohol dependence and ALD.[124] The ALDH2*2 allele produces an ALDH2 variant with greatly reduced enzymatic activity and delayed aldehyde metabolism, and a lower risk of developing alcohol addiction; a meta-analysis of data related to Asian populations found that the presence of the ALDH2*2 allele was associated with a lower frequency of alcohol dependence and ALD.[125] The frequency of the ALDH2*2 allele was significantly lower among Korean patients with alcoholic liver cirrhosis than among those without it.[126,127] Mutation of the gene encoding patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) has been suggested as a genetic risk factor for ALD, with a higher frequency of *PNPLA3* rs738409 GG found in a high-risk group for progression to ALD.[128] Two recent meta-analyses have provided evidence of an association between genetic polymorphisms in the gene encoding interleukin (IL)-10 and alcoholism,[129] and an increased risk of ALD among alcoholics with allelic variants of the gene encoding glutathione-*S*-transferase.[130] However, these candidate genes have not been confirmed in Korean studies. Studies of ALD have thus far been limited to identifying specific genetic mutations, indicating a need for genome-wide association analyses.

Viral factors

The prevalence of hepatitis C virus (HCV) is higher among alcoholics than non-alcoholics, and the combination of HCV and alcohol has a synergistic effect on liver injury.[131] Possible underlying mechanisms for this include immune suppression, stimulation of viral replication, increased oxidative stress, and hepatocyte cytoxicity. Alcohol intake by patients with HCV infection increases the risk of liver cirrhosis and HCC,[132,133] and reduces their responses to interferon treatment.[134]

Unlike for HCV, data is limited regarding the association between hepatitis B virus (HBV) and progression of liver disease due to alcohol consumption. Nevertheless, alcohol consumption does have an adverse effect on hepatitis patients.[135] Specifically, alcohol directly affects host-cell metabolism and gene expression, which acts to increase the expression and replication of viral genes.[136] Therefore, patients with HBV should avoid consuming alcohol.[97]

Smoking

Smoking is a risk factor for ALD, causes oxidative stress, and accelerates fibrosis in patients with ALD.[137] Abstaining from smoking is therefore recommended in patients with ALD.

Coffee

Many studies have found that the risk of ALD reduces as coffee consumption increases, and that coffee may suppress the development of ALD.[138-141] A marked decrease in mortality due to liver disease was found among those who drink three or more cups of coffee per day compared to those who drink two or fewer cups per day.[142] The consumption of caffeinated drinks other than coffee is not associated with a decreased incidence of liver cirrhosis, which suggests that substances other than caffein in coffee have an important role in ALD.[140]

[Recommendations]

4. Excessive drinking, defined as an average alcohol consumption exceeding 40 g/day in men and 20 g/day in women, increases the risk of alcoholic liver injury and should be avoided. (A1)

5. Daily or binge drinking increases the risk of ALD and should be avoided. (A1)

6. Alcohol abstinence is necessary for patients with chronic viral hepatitis. (B1)

7. Obesity and smoking increase ALD, and so weight control and smoking cessation are recommended. (B1)

Future research

1. There is a need to characterize cases of ALD that are accompanied by other liver diseases such as viral hepatitis.

2. There is a need to assess the interactions between the risk factors for ALD.

3. There is a need for genome-wide association studies involving patients with ALD.

PATHOPHYSIOLOGY OF ALCOHOLIC LIVER DISEASE

The pathophysiology of ALD varies according to the stage of the disease and the presence of genetic and non-genetic factors affect the onset and clinical progression of ALD.[143] Most studies of chronic alcohol consumption have been based on rodent-based

models, and because these experiments only cause moderate degrees of liver disease, fibrosis, and injury, the mechanism underlying the pathophysiology of ALD in humans has not yet been fully elucidated.[144]

Alcoholic fatty liver (steatosis)

Steatosis is the initial reaction to alcohol abuse and is characterized by the adiposis of hepatocytes. Alcoholic fatty liver occurs through many complex mechanisms, via the following four steps.[144] First, alcohol oxidation leads to increases in the synthesis of nicotinamide adenine dinucleotide (NADH), triglycerides, and fatty acids, and to the suppression of mitochondrial β-oxidation.[145] Second, there is an increase in the influx of free fatty acids from the adipose tissue and chylomicrons from the visceral mucosa into the liver.[145] Third, ethanol mediates the suppression of adenosine-monophosphate-activated protein kinase (AMPK) activation, resulting in an increase in lipid biosynthesis, suppression of peroxisome proliferator-activated receptor α (PPARα), and decrease in lipolysis due to the activation of sterol regulatory element binding protein 1c (SREBP1c).[146-148] Fourth, there is acetaldehyde-induced mitochondria and microtubule damage, resulting in decreased NADH oxidation and accumulation of very-low-density lipoprotein (VLDL).[145]

Alcoholic steatohepatitis

Steatohepatitis is defined as a condition with fatty liver, inflammatory cell infiltration comprising mainly polymorphonuclear leukocytes, and hepatocyte injury. In ALD, although alcoholic steatohepatitis is a necessary step in the progression to liver fibrosis and cirrhosis, liver fibrosis is not included in the definition of steatohepatitis.[43] Currently, there is no consensus on the pathologic classification of steatohepatitis, and the severity of this condition is determined by environmental factors such as the quantity of alcohol consumed, lifestyle, and dietary habits.[43]

Various factors affect the onset of alcoholic steatohepatitis. First, the toxic effect of acetaldehyde and the production of oxygen free radicals affect the development of this condition. Ethanol is metabolized into acetaldehyde by ADH within the cytosol, P450 within the microsomes, and catalase within the peroxisomes. Ethanol metabolism results in the production of oxygen free radicals, peroxidation of lipids, and a decrease in mitochondrial glutathione and S-adenosyl-L-methionine (SAMe) levels, and these metabolites sensitize the hepatocyte to injury. Acetaldehyde is then metabolized by mitochondrial ADH into acetate, which combines with protein and DNA to alter their function, ultimately affecting protein synthesis.[149,150] These products then act as auto-antigens to activate the immune system, increasing the lymphocyte count and causing liver injury. Furthermore, acetaldehyde causes oxidative stress and apoptosis through mitochondrial damage and impairment of glutathione function.[151]

Second, there are pro-inflammatory cytokines. Alcohol metabolites and oxygen free radicals stimulate the signal-transduction pathways related to nuclear factor-κB (NFκB), signal transducer and activator of transcription-Janus kinase (STAT-JAK), and c-Jun N-terminal kinase (JNK), which induce the production of inflammation mediators such as tumor necrosis factor-α (TNF-α), IL-17, CXC chemokines, and osteopontin.[152] Alcohol abuse disrupts the normal intestinal microbiota and increases the permeability of the endotoxins produced by intestinal bacteria, increasing serum lipopolysaccharide levels,[153] and causing an inflammatory reaction in Kupffer cells via the CD14/toll-like receptor 4 (TLR 4) pathway.[154] This inflammatory environment in ALD causes the infiltration of polymorphonuclear leukocytes, production of oxygen free radicals, and hepatocyte injury.

Fibrosis in alcoholic liver disease

Liver fibrosis is a recovery response seen in every form of chronic liver injury, and is characterized by the excessive accumulation of extracellular matrix proteins such as collagen.[155,156] Fibrosis can occur in alcoholic steatohepatitis, and occurs mainly where ADH is located, typically in pericentral and perisinusoidal regions.[155] In the progression stage, collagen bands become apparent and bridging fibrosis develops. This stage precedes liver cirrhosis and the formation of regeneration nodules. The cytological and molecular biological mechanism of fibrosis in ALD is currently not well understood.[120]

Metabolites of alcohol such as acetaldehyde directly activate hepatic stellate cells (HSCs), the main producers of collagen in the injured liver, and play a major role in the production of portal fibroblasts and bone-marrow-derived myofibroblasts.[155,156] HSCs are also activated by injured hepatocytes, activated Kupffer cells, and infiltration of polymorphonuclear leukocytes. These cells secrete growth factors such as transforming growth factor-β1 (TGF-β1) and platelet-derived growth factor (PDGF), cytokines such as leptin, angiotensin II, IL-8, and TNF-α, soluble mediators such as nitric oxide, and oxygen free radicals. Importantly, oxygen free radicals stimulate the signaling pathway within HSCs, which includes extracellular signal-regulated kinase, phosphoinositide 3

kinase (PI3K)/Akt, and JNK.[157] These oxygen free radicals also enhance the activity of tissue inhibitor of metalloproteinase 1, reducing the activity of metalloproteinases and stimulating the accumulation of extracellular matrix proteins such as collagen.

Future research

1. There is a need to study how genetic differences influence the progression of liver fibrosis.

CLINICAL DIAGNOSIS OF ALCOHOLIC LIVER DISEASE

For the diagnosis of ALD, the presence of heavy drinking, which is a prerequisite, must be confirmed through history and questionnaires and may be supplemented by blood tests. Identifying liver disease might require methods such as a physical examination, blood tests, and radiologic studies, and a liver biopsy may also be performed under certain circumstances.

History taking

The type of alcoholic beverage, quantity of alcohol consumed, weekly drinking frequency, and duration of drinking are all important data to obtain during history-taking. Since patients frequently deny or underreport the amount of drinking, it is helpful to obtain the drinking history through questionnaires or from family members. Although currently there is no consensus on the minimum amount of alcohol required for ALD, a cutoff that is often applied is an average alcohol intake exceeding 40 g/day in men and 20 g/day in women.[97,158-160] The average daily alcohol intake is calculated using the following equation: [amount consumed (mL)×alcohol by volume (%)×specific gravity of alcohol (0.785)×number of drinking days per week]÷7. For example, if a person drinks one Soju bottle (360 mL, 19% alcohol by volume) three times a week, then the amount consumed would be (360 mL×19%×0.785)÷100 =53.7 g, and the average daily alcohol intake would be (53.7 g×3)÷7=23 g. The alcohol contents of various forms of alcoholic beverage are listed in Table 3.

A standard drink in Korea contains 12 g of alcohol (as defined by the Ministry of Health and Welfare), and so is approximately equal to 1.5 nips of Soju (90 mL), 1 can of beer (355 mL), 1 bowl of Makgeolli (230 mL), 1 glass of wine (120 mL), or 1 nip of whisky (40 mL).

Symptoms and signs

The effects of ALD can range from being asymptomatic to liver failure and death. While symptoms and signs such as epigastric discomfort, fever, fatigue, anorexia, malaise, weight loss, tender hepatomegaly, jaundice, spider angiomata, cachexia, gynecogenic changes, and right upper-quadrant abdominal bruit may occur, they are nonspecific.[160-162] In severe alcoholic hepatitis or liver cirrhosis, symptoms and signs such as ascites, lower extremity edema, hepatic encephalopathy, and esophageal variceal bleeding may be seen.[163] Damage to organs other than the liver may manifest as gastritis, peptic ulcer, pancreatitis, neuropathy, myopathy, Dupuytren's contracture, cardiomyopathy, arrhythmia, anemia, parotid gland hypertrophy, lacrimal gland hypertrophy, altered mental status due to delirium tremens, and sleep disorders.[164-169]

Blood tests

Blood tests for detecting a history of chronic alcohol consumption include serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltranspeptidase (GGT), mean corpuscular volume (MCV), and carbohydrate deficient transferrin (CDT).[170-172] Combining the results of several of these tests is superior to using any single test.[173] In ALD, AST elevation is more prominent than that of ALT, but the levels of AST and ALT usually do not exceed 300 IU/L. Alcoholic hepatitis may be suspected when the AST/ALT ratio exceeds 2,[174,175] and has a very high probability when it exceeds 3.[176] Because GGT is elevated by alcohol

Table 3. Alcohol contents of different types of alcoholic beverage

Type	Volume (mL/bottle)	Alcohol by volume (%)	Alcohol amount (g)
Soju	360	19	54
Makgeolli	750	6	35
Beer	355	4.5	12
Wine	700	12	66
Whisky	360	40	113

consumption in about 75% of habitual drinkers, it is useful to determine whether a patient with ALD has indeed abstained from drinking.[177,178] However, care must be exercised since GGT may also be elevated due to non-alcoholic liver disease, obesity, diabetes, smoking, or drug use.[179,180] In general, GGT levels recover slowly following abstinence from alcohol. MCV may also be elevated by heavy drinking, and is occasionally observed when the daily alcohol consumption exceeds 60 g.[181,182] While MCV elevation alone has a low sensitivity, this is increased when accompanied by GGT elevation or when the levels decrease following treatment;[183] MCV returns to normal after several months of abstinence.[184] While CDT is known as a useful biochemical marker for heavy drinking,[170,171,185,186] it is not a popular measure due to its high specificity but low sensitivity.[187] Other findings seen with progression of liver disease include a decrease in serum albumin, increase in bilirubin, prolonged prothrombin time, and decrease in platelet count.

Radiologic tests

Radiologic tests can be used to identify steatosis, evaluate the progression of liver disease and the presence of complications, and rule out diseases such as biliary tract disease and liver tumors.[188] However, radiologic tests alone cannot be used for the definitive diagnosis of alcohol as the cause of liver disease. Ultrasonography is useful for identifying steatosis, and findings such as liver morphology and splenomegaly can be used to evaluate the progression of liver disease.[189] Although abdominal computed tomography (CT) scans and magnetic resonance imaging (MRI) are more accurate than ultrasonography for evaluating steatosis, there currently are no standardized test protocols and these methods are costly.[190,191] Liver elastography may be used to indirectly evaluate the degree of fibrosis in ALD. This test is based on the correlation between liver stiffness due to fibrosis and liver elasticity, and employs ultrasonography or MRI.[192-194] While these tests have the advantage of being noninvasive, they are also non-standardized and care must be exercised when interpreting the results since the presence of steatosis and severe inflammation may interfere with correct interpretations.

Histologic diagnosis

Histologic findings

A liver biopsy is the standard test for making a definitive diagnosis of ALD and evaluating the inflammatory activity and fibrosis stage. Common histologic findings in ALD include steatosis, hepatocyte injury, lobular inflammation, Mallory-Denk bodies, megamitochondria, ductular proliferation, ductular bilirubinostasis, intraparenchymal cholestasis, fibrosis, and liver cirrhosis.[44,195] Although histologic findings are sometimes used to classify ALD into simple steatosis or fatty liver, steatohepatitis, hepatic fibrosis, or liver cirrhosis, it is possible for these conditions to coexist in a patient, and currently there is no definitive classification scheme for these findings.

Alcoholic fatty liver is the most common finding in ALD, wherein hepatocytes exhibit typical macrovesicular steatosis characteristics such as cell expansion due to large fat droplets, and displacement of the nucleus toward the cell membrane.[196] These changes first appear in the central zone of the lobule and progress over time to eventually encompass the entire lobule.[196] The ballooning degeneration of hepatocytes is occasionally accompanied by apoptotic bodies. Mallory-Denk bodies, the eosinophilic and crescentic aggregation of intermediate filaments and other proteins around the nucleus, may also be seen.

Specific histologic characteristics of alcoholic steatohepatitis include steatosis, ballooning degeneration of hepatocytes, and lobular infiltration by inflammatory cells, especially by polymorphonuclear neutrophils.[197] Megamitochondria and Mallory-Denk bodies, although not specific for ALD, are nonetheless suggestive of active drinking. Periportal ductular proliferation, ductular bilirubinostasis, and intraparenchymal cholestasis may also be observed. Fibrous tissue may begin to accumulate around the terminal hepatic vein in the lobular central zone, and then progress to perisinusoidal and pericellular areas, resulting in the characteristic "chicken-wire fibrosis." Sclerosing hyaline necrosis refers to hepatocyte necrosis in zone 3 accompanied by perivenular and perisinusoidal fibrosis. The occurrence of terminal hepatic vein occlusion and sinusoid narrowing will increase the portal pressure and thicken the fibrous septum, ultimately resulting in the micronodular form of liver cirrhosis.[198]

Clinical application of liver biopsy

A liver biopsy is performed percutaneously with sonographic guidance or via the jugular vein; the latter approach is used when a percutaneous liver biopsy is contraindicated due to severe coagulopathy or moderate-to-severe ascites.[199] A liver biopsy carries the risk of complications such as intraperitoneal hemorrhage and abdominal pain, and may be fatal in rare instances. Furthermore, the accuracy of a liver biopsy is limited by factors such as sampling error and interobserver variation.

A liver biopsy, while not necessary for diagnosis or treatment, is useful for establishing an ALD diagnosis and for assessing the severity of disease to predict the prognosis in all patients with suspected ALD.[200,201] Around 20% of alcohol abusers with abnormal liver function tests were found to have etiologies other than alcohol, and only 70% of patients with suspected severe alcoholic hepatitis were definitively diagnosed with alcoholic hepatitis using a liver biopsy.[202] In patients with severe alcoholic hepatitis, the existence of severe inflammation was a useful marker for whether treatment with steroids would be effective.[203] In patients with a diagnosis of alcoholic steatohepatitis without sepsis, severe intraparenchymal cholestasis, along with Maddrey's discriminant function (DF) score, was an independent predictor for short-term mortality.[204] Also, in patients with acute exacerbation of alcoholic liver cirrhosis, early liver biopsy was useful for confirming the diagnosis of alcoholic hepatitis as well as estimating the prognosis.[205]

A liver biopsy is rarely performed for the diagnosis and treatment of ALD in Korea. However, for patients with severe alcoholic hepatitis who may need specific medical treatment such as corticosteroids, a liver biopsy may be considered for a definitive diagnosis and for determining the prognosis.

Classification and clinical features of alcoholic liver disease

The diagnosis of ALD may be made in patients with a daily alcohol consumption exceeding 40 g in men and 20 g in women, with clinical, laboratory, radiological, or histological evidence of liver disease, and in whom other etiologies for liver injury can be excluded. Although excluding other etiologies of liver disease such as viral hepatitis, non-alcoholic fatty liver disease, and drug-induced liver injury is helpful for diagnosing ALD, because it is possible that more than one etiology is present, it is important to identify which is the main lesion. ALD is categorized based on the underlying pathology into alcoholic fatty liver, alcoholic hepatitis, and alcoholic liver cirrhosis (Table 4).[206] While exclusive forms do exist, overlapping clinical features are seen in most cases.

Alcoholic fatty liver is usually asymptomatic. In blood tests, AST, ALT, or bilirubin levels may be normal or mildly elevated.[160] While these values typically return to normal following several weeks of alcohol abstinence,[195] in some cases the disease may progress to liver fibrosis or cirrhosis.[50]

Alcoholic hepatitis presents with various clinical features. In mild cases it is difficult to distinguish alcoholic hepatitis from alcoholic fatty liver, while in severe cases alcoholic hepatitis carries a high risk of death due to liver failure. Liver fibrosis may lead to portal hypertension, making it difficult to distinguish it from liver cirrhosis.[163] Blood tests may reveal anemia, leukocytosis, and thrombocytopenia, and the AST/ALT ratio typically exceeds 2.[175,176,207] While these clinical features usually resolve following abstinence, they may last more than 6 months in severe alcoholic hepatitis.

Alcoholic liver cirrhosis and liver cirrhosis due to other etiologies share similar clinical features.[208] While it is not uncommon to be asymptomatic, anorexia and malnutrition due to habitual drinking can result in weight loss and skeletal muscle atrophy. Progression of liver cirrhosis may cause spider angioma, gynecomastia, and jaundice, and portal hypertension may result in variceal bleeding, ascites, and hepatic encephalopathy. Even in alcoholic liver cirrhosis, alcohol abstinence and proper nutrition can result in improved clinical features.[48]

[Recommendations]

8. Thorough history-taking for details such as the amount, frequency, duration, and type of drinking is necessary to make a diagnosis of ALD. (A1)

9. With adequate history of excessive drinking and clinical evidence for liver disease, the diagnosis of ALD can be made. In patients with severe alcoholic hepatitis requiring corticosteroid treatment, a liver biopsy should be considered for both a definitive diagnosis and estimation of prognosis. (B1)

Future research

1. There is a need to evaluate the usefulness of a liver biopsy in ALD.

2. There is a need for standardized histological criteria for the classification and evaluation of the severity of ALD.

3. There is a need to develop noninvasive diagnostic methods for ALD.

PROGNOSIS EVALUATION FOR ALCOHOLIC LIVER DISEASE

Evaluation of the prognosis for ALD focuses mainly on alcoholic hepatitis. Severe alcoholic hepatitis is traditionally defined as having a DF score of ≥32 or as having the evidence of hepatic encephalopathy. Severe alcoholic hepatitis has a poor prognosis

Table 4. Clinical features of alcoholic liver disease

		Alcoholic fatty Liver	Alcoholic hepatitis	Alcoholic liver cirrhosis
Symptoms and signs		Mostly asymptomatic, hepatomegaly	Jaundice, fever, tender hepatomegaly	Spider angioma, palmar erythema, jaundice
	Complications of portal hypertension (variceal bleeding, ascites, encephalopathy)	–	+/–	+/–
Blood tests	Leukocytosis	+/–	+	–
	Macrocytosis	+/–	+	+
	Thrombocytopenia	+/–	+	+
	AST or ALT ↑*	+/–	++	+/–
	AST/ALT ratio >1	+/–	+ ~ ++	++
	Hyperbilirubinemia	–	– ~ ++	– ~ ++
	Hypoalbuminemia	–	– ~ +	–~ ++
	PT prolongation	–	– ~ ++	– ~ ++
Imaging studies†		Fatty liver± hepatomegaly	Fatty liver, hepatomegaly±ascites	Nodular surface, splenomegaly, varix, ascites
Histology		Steatosis	Steatosis, hepatocellular ballooning, PMNL infiltration, Mallory bodies, perisinusoidal fibrosis	Cirrhotic nodule

PMNL, polymorphonuclear leukocyte; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time.
*Usually <300 IU/L.
†Ultrasonography, computed tomography, and magnetic resonance imaging.

without treatment, with a 28-day mortality rate of 30-50%.[203] In patients with alcoholic hepatitis of all severities, early prognosis stratification and treatment decisions are important for improving the prognosis.

Various prognostic models in patients with alcoholic hepatitis have been developed over the past decades, such as the DF score, Model for End-Stage Liver Disease (MELD) score, Glasgow Alcoholic Hepatitis Score (GAHS), and the ABIC (Age, Bilirubin, International Normalized Ratio, Creatinine) score (Table 5).

The DF score was first introduced in 1978 in a clinical trial assessing the treatment response to corticosteroids in patients with alcoholic hepatitis, and was modified slightly in 1989. The modified DF (mDF) score has been widely used for stratifying the severity of alcoholic hepatitis in practice.[209] Patients with alcoholic hepatitis and an mDF score of <32 had a survival rate of 90%, while those with an mDF score of ≥32 had a survival of rate of 50-65%.[210]

The MELD score was initially developed to estimate the prognosis in patients who had undergone the transjugular intrahepatic portosystemic shunt (TIPS) procedure, and was later adopted as a model for selecting candidates for liver transplantation.[211] Several studies have investigated the utility of the MELD score for assessing the prognosis of patients with ALD, albeit with different cutoff values.[212-215] One study proposed that a MELD score of 21 provided high sensitivity and specificity in detecting patients with a poor prognosis. The MELD score was found to be a more useful predictor of prognosis in patients with accompanying ascites or hepatic encephalopathy.[212,213]

The GAHS was developed to overcome the limitations of other models in assessing the prognosis of patients with alcoholic hepatitis, such as the low specificity of the mDF score and the unclear cutoff value for the MELD score.[216] In patients with an mDF score of ≥32, those with a GAHS of <9 gained no survival benefit with steroid treatment, while those with a GAHS of ≥9 had a poor prognosis without steroid treatment. Therefore, the GAHS may be useful for identifying a subgroup of patients who may derive benefit from corticosteroids among patients with an mDF score of ≥32.[217]

The ABIC model was constructed using four components: age, serum bilirubin, prothrombin time, and serum creatinine. Using

Table 5. Prognostic models in patients with alcoholic hepatitis[203,212,217,218,226]

Scoring system	Formula				Test characteristics
Pretreatment model					
mDF	$4.6\times[PT_{patient}-PT_{control}$ (seconds)]+serum total bilirubin (mg/dL)				Typically 30-50% mortality within 28 days if score ≥32
MELD[*]	$9.57\times\log_e[Cr$ (mg/dL)]$+3.78\times\log_e$ [bilirubin (mg/dL)]$+11.20\times\log_e(INR)+6.43$				Typically 20% mortality in 90 days if score >21
GAHS	Score	1	2	3	Greater than 50% mortality in 28–84 days if score ≥9 (for score calculated on hospital day 1 or day 7)
	Age (years)	<50	≥50		
	WCC (109/L)	<15	≥15	–	
	Urea (mmol/L)	<5	≥5	–	
	PT ratio	<1.5	1.5–2.0	>2.0	
	Bilirubin (mol/L)	<125	125–250	>250	
ABIC	[age (years×0.1)]+[serum bilirubin (mg/dL)×0.08]+[serum Cr (mg/dL)×0.3]+(INR×0.8)				Stratification of risk of death in patients with alcoholic hepatitis at 90 days and 1 year
On-treatment model					
Lille model[†]	$R=3.19-0.101\times[age$ (years)]$+0.147\times[albumin$ on day 0 (g/L)]$+0.0165\times[evolution$ in bilirubin level (μmol/L)]$-0.206\times$renal insufficiency$-0.0065\times[bilirubin$ on day 0 (μmol/L)]$-0.0096\times[PT$ (seconds)] Lille score $= \exp(-R)/[1+\exp(-R)]$ Note: Renal insufficiency rated 0 if absent and 1 if present (below or above 1.3 mg/dL, respectively). Evolution in bilirubin level is bilirubin level on day 0 minus that on day 7.				Typically 75% mortality within 6 months if score ≥0.45 in patients on corticosteroid therapy

mDF, modified discriminant function; MELD, Model for End-Stage Liver Disease; Cr, creatinine; INR, international normalized ratio; GAHS, Glasgow Alcoholic Hepatitis Score; WCC, white cell count; ABIC, Age, Bilirubin, INR, Creatinine.
[*]See http://www.mayoclinic.org/meld/mayomode17.html
[†]See http://www.lillemodel.com.

cutoff values of 6.71 and 9.0, the ABIC model divided patients with alcoholic hepatitis into those with a low, intermediate, and high risk of death at 90 days, which was also useful in predicting mortality at 1 year.[218] Patients with an intermediate risk of death may benefit from corticosteroid or pentoxifylline therapy.[218]

One study found the hepatic venous pressure gradient (HVPG) to be higher in patients who died due to alcoholic hepatitis than in those who survived, while another study found no association between HVPG and the short- or long-term prognosis of patients with alcoholic hepatitis.[219,220] Further research on this subject is needed.

Some studies have found that the prognosis in patients with alcoholic hepatitis can be estimated more accurately from the Child-Turcotte-Pugh (CTP) score and the mDF score than from the MELD score,[221] but most studies show that the mDF and MELD scores are more predictive than the CTP score. Hence, the CTP score is not usually used for estimating prognosis in alcoholic hepatitis.[213,220,222]

Korean studies have found the mDF score to be an independent prognostic factor for alcoholic hepatitis, with the MELD score yielding comparable results.[47] Based on recent studies, the mDF, MELD, ABIC scores, and GAHS appear to be better prognostic models than the CTP score. All of the models were found to be good predictors of short-term mortality but poor predictors of long-term mortality.[220] Based on these studies, the mDF and MELD scores are useful for predicting short-term mortality and guiding treatment decisions in patients with severe alcoholic hepatitis. The GAHS and the ABIC score also show potential as prognostic models for alcoholic hepatitis.[47,222,223]

With respect to predicting survival in patients treated with corticosteroids, early change in bilirubin level (ECBL; defined as a change in bilirubin levels after 1 week of treatment) and the Lille model based on ECBL are notable and are described in the following section.[47,224-226]

[Recommendation]

10. The mDF score and the MELD score are useful for determining the prognosis and guiding treatment in patients with alcoholic hepatitis. (A1)

Future research

1. There is a need for clinical models that predict poor prognosis among patients with an mDF score of <32.

TREATMENT FOR ALCOHOLIC LIVER DISEASE

The treatment for ALD varies depending on the stage of the disease. For alcoholic fatty liver, abstinence or controlled drinking is the most important treatment. The various treatment approaches for alcoholic hepatitis are described in separate section. For alcoholic liver cirrhosis, treatment involves abstinence and following the KASL Clinical Practice Guidelines for Liver Cirrhosis.

Therapy for alcohol withdrawal syndrome

AWS refers to the group of symptoms and signs that occur 6-24 hours following the abrupt cessation of alcohol consumption among those who habitually drink excessively. Symptoms and signs include those of autonomic nervous system activation such as tachycardia, sweating, and hand tremor, gastrointestinal symptoms such as nausea and vomiting, and if severe, deficits in cognitive function such as hallucinations, seizures, and withdrawal delirium that may lead to death. Alcohol withdrawal seizure is a rebound phenomenon that can occur following the abrupt cessation of alcohol consumption that is due to a lowered seizure threshold. Because there is no need for anticonvulsants in patients with alcohol withdrawal seizure, it is necessary to distinguish it from genuine seizure. Delirium tremens is a serious complication of AWS, typical symptoms of which include altered mental status, disorientation to person, place, or time, and intra- and inter-daily variations of symptoms.[227] The symptoms are typically worst at 3-5 days following the abrupt cessation of alcohol consumption. Signs of autonomic nervous system activation such as high fever, tachycardia, hypertension, and sweating, as well as comorbidities such as dehydration, electrolyte imbalance, renal failure, head trauma, infection, gastrointestinal bleeding, pancreatitis, and liver failure should be carefully and strictly evaluated, and frequent monitoring of vital signs is necessary.[228]

The Clinical Institute Withdrawal Assessment for Alcohol (CIWA) is known to be helpful for evaluating the severity of AWS, treatment planning, and facilitating objective communication between healthcare providers. However, high scores may be seen in psychiatric conditions that are similar to AWS, such as anxiolytic withdrawal, anxiety disorder, and physical conditions such as sepsis, hepatic encephalopathy, and severe pain.[228] For this reason, the CIWA protocol is not recommended for a diagnosis of AWS.[228]

A comparison of inpatient versus outpatient treatment revealed that outpatient treatment was more cost-effective, but there was no difference in the alcohol abstinence rate at 6 months.[229] If there are serious complications of AWS such as delirium, seizures, or physical and/or psychological comorbidities, admission and inpatient treatment is recommended, with treatment goals of symptomatic relief without complications and maintenance of abstinence as a long-term treatment. Therefore, psychiatric consultation is recommended for the evaluation and acute management of AWS and long-term abstinence planning.

For pharmacological treatment, long-acting benzodiazepines (e.g., chlordiazepoxide and diazepam) are recommended for the prevention of seizures, with effects such as anxiety relief, sedation, and somnolence via activation of gamma-aminobutyric acid (GABA).[230] Lorazepam, which is an intermediate-acting benzodiazepine, is recommended for patients with severe AWS, advanced age, recent head trauma, liver failure, respiratory failure, other serious medical comorbidities, or obesity. Lorazepam is started at a dosage of 6-12 mg/day and tapered off following resolution of the withdrawal symptoms (Table 6).[231,232]

Diminished cognitive function due to thiamine deficiency is common in patients with alcohol use disorder; thiamine should thus be given to all patients with AWS (100-300 mg/day) and maintained for 2-3 months following resolution of their withdrawal symptoms.[233]

[Recommendations]

11. For AWS, psychiatric consultation is recommended for the evaluation, treatment, and long-term planning of alcohol abstinence. (A1)

12. Inpatient treatment is recommended for cases with serious complications such as alcohol withdrawal delirium or seizures. (A1)

13. Benzodiazepines should be used to treat AWS. (A1)

Table 6. Treatment of alcohol withdrawal syndrome (AWS)[227,228,230-232]

General management		
Indications for admission	Significant AWS, high levels of recent drinking, history of withdrawal seizures or delirium tremens, co-occurrence of a serious medical or psychiatric illness, or failure of outpatient treatment	
Conservative treatment	Fluids, electrolytes (especially magnesium), vitamins, and a comfortable environment	
Pharmacological treatment		
Thiamine[*]	Prevention of Wernicke encephalopathy: 100–300 mg/day for 4–12 weeks Management of Wernicke encephalopathy: 100–500 mg/day for 12–24 weeks	
Benzodiazepines[†]		
Chlordiazepoxide	PO	25–100 mg every 4–6 hours
Diazepam	PO/IV/IM	5–10 mg every 6–8 hours
Lorazepam	PO/IV/IM	1–4 mg every 4–8 hours
Other drugs		
Carbamazepine[‡]	PO	200 mg every 6–8 hours
Haloperidol[§]	PO/IM	0.5–5 mg every 8–12 hours, PO; 2–5 mg, IM

PO, per oral; IV, intravenous; IM, intramuscular administration.
[*]Thiamine should be given before administering IV fluids containing glucose, since the IV administration of glucose may precipitate acute thiamine deficiency.
[†]Dosage and routes given for a standard fixed-dose regimen, which includes dose tapers over time.
[‡]Alternative to benzodiazepine that is effective in seizure prevention.
[§]To be used carefully as adjunctive therapy only in cases of agitation or psychotic symptoms such as hallucinations that are not controlled by benzodiazepine.

ALCOHOL ABSTINENCE

Alcohol abstinence is the most important treatment for patients with ALD,[76,234] since it improves their survival and prognosis and prevents the progression to liver cirrhosis through histologic improvements and a reduction in portal pressure.[48,235,236] Many treatment methods are currently being used to help maintain abstinence.[237]

Pharmacologic treatment

While many drugs have been used to promote alcohol abstinence among patients with alcohol use disorder, the use of these agents is limited to those with liver-function abnormalities (liver-function tests: >3×normal increase in bilirubin) or renal failure. There are few studies that target ALD patients with the exception of baclofen. More studies are required to obtain evidence of their efficacy and safety in patients with ALD.

Baclofen is a GABAB receptor agonist that is used as a muscle relaxant.[238] A study involving patients with liver cirrhosis found that a 12-week course of baclofen effectively maintained abstinence by reducing the craving for alcohol.[239] Further studies should investigate the use of baclofen for abstinence in patients with ALD.[240,241]

Acamprosate reduces the withdrawal effects of and the craving

for alcohol. The desired concentration for acamprosate is reached within 1-2 weeks of initiating treatment and it is effective at maintaining abstinence in alcohol-dependent patients following withdrawal.[242,243] Treatment is initiated 3-7 days following the last episode of alcohol consumption and started after withdrawal symptoms have resolved. With respect to dosage, 1,998 mg/day is given to patients with a body weight of ≥60 kg and decreased by a one-third for those with a body weight of <60 kg, for a total treatment period of 3-6 months.[244-246]

Naltrexone decreases the concentration of dopamine in the brain and dampens activation of the reward pathway by alcohol, thereby decreasing excessive drinking and recurrence rates and increasing abstinence duration in patients with alcohol dependence.[247,248] With respect to dosage, 25 mg is given during the first 1-3 days and increased to 50 mg thereafter, with a typical total treatment period of 3-6 months, but this can also last for up to 12 months.[249] Because there is risk of toxic liver injury, naltrexone is not recommended in patients with ALD.

Disulfiram is an inhibitor of ALDH that causes a buildup of acetaldehyde in the body following alcohol consumption.[250] Since the buildup of acetaldehyde results in unpleasant symptoms such as flushing, dizziness, nausea, vomiting, arrhythmia, dyspnea, and headache, it is known as an aversive therapy and is currently not commonly used.

Psychosocial treatment

The goal of psychosocial treatment is to allow the patient to understand and obtain insight into his or her pathological pattern of drinking. Active psychological support should be provided with focus on the environment, reasons, and expected consequences of drinking, and should be accompanied by family and group therapy as well.[251,252]

The aim of individual psychotherapy for a patient with alcohol dependence is to establish a therapeutic plan by careful psychiatric evaluation and select treatment modalities such as individual interview, psychoeducation, group therapy, and cognitive behavioral therapy. The treatment principles of alcohol dependence involve (1) allowing the patient to accept his or her lack of control over alcohol, (2) providing education regarding alcohol dependence, and (3) helping the patient to achieve control over him- or herself in order to maintain abstinence. This sort of treatment should not end as part of inpatient treatment, but instead should be continued after discharge to prevent recurrence. It is therefore important that patients with alcohol dependence actively get involved in group therapy such as Alcoholics Anonymous. This group meets on a nationwide basis and makes it possible to reduce the craving for alcohol and maintain healthy abstinence through peer support.

Social support from family and friends is also necessary for successful therapy. Alcohol dependence is a dysfunctional family disorder, in that in many cases it is not only the patient who needs treatment but also family members who are subject to abuse from the patient. Both the patient and his or her family may benefit from active involvement in family education and therapy. Community alcohol counseling centers provide regular abstinence meetings, family meetings, and psychoeducation; coordination with these facilities may prove very helpful.

Other methods of psychosocial treatment include motivational enhancement, 12-step facilitation therapy, cognitive behavioral therapy, social skills training, and coping skills training. Behavioral therapy involves training the patient to use methods other than alcohol to alleviate anxiety, and includes interventions such as relaxation therapy and assertive training. Psychiatric consultation is recommended for psychosocial treatment.

Brief interventions are effective methods that involve providing pertinent evaluation, information, and advice to reduce risky drinking behavior and risk of ALD.[253] Commonly used brief interventions include motivational interviewing and counseling over a short time span. A brief intervention is delivered in a structured fashion, among which the FRAMES (Feedback, Responsibility, Advice, Menu, Empathy, Self-efficacy) model is representative. The FRAMES method involves feedback about the dangers of continued drinking, emphasizes the drinker's responsibility in assuming the choices and consequences of drinking, advises abstinence, provides a menu of alternatives, empathizes with the drinker's perspective, and encourages self-motivation for abstinence.[254-256] Brief interventions have been reported to lower morbidity and mortality related to drinking, and to be an effective non-pharmacologic approach for abstinence.[256,257] Brief interventions may be implemented in various healthcare settings, such as the inpatient or outpatient setting, private clinic, or public healthcare settings such as community counseling centers, or even healthcare services in the workplace and universities. It is a cost-effective method at a primary medical institution and is effective in patients with mild ALD.[253,258]

[Recommendations]

14. In patients with ALD, alcohol abstinence is the most important treatment. (A1)

15. In patients with ALD, pharmacologic and psychosocial treatment can be implemented to achieve alcohol abstinence. (B2)

16. In patients with ALD, baclofen and acamprosate can be used to achieve alcohol abstinence. (B2)

17. In hazardous drinkers and patients with alcohol use disorder, brief interventions should be implemented to encourage abstinence or controlled drinking. (A1)

Future research

1. There is a need to evaluate the efficacy of combined therapy of baclofen and psychosocial therapy for alcohol abstinence in ALD.

2. There is a need to identify effective brief intervention methods.

3. There is a need to evaluate the efficacy and safety of naltrexone and acamprosate in ALD.

4. There is a need to evaluate new pharmacologic treatments for abstinence in ALD.

NUTRITIONAL THERAPY

Many patients with ALD are malnourished, and the complications of ALD are significantly associated with the nutritional status.[107,259] This has prompted many studies to evaluate the effect of

nutritional support in ALD patients.[260,261] While active nutritional support is known to improve biochemical markers and the nutritional status of ALD patients, it is not clear whether it also improves their survival rate.[260,262]

Patients with severe alcoholic hepatitis who received parenteral nutrition had higher early mortality rates but lower late mortality rates than those receiving steroid treatment, with the net result being no difference in their overall mortality rates.[263]

Long-term supplementation with branched-chain amino acids is known to improve nitrogen balance and yield improvements in hepatic encephalopathy and liver function tests.[264] Branched-chain amino acid supplementation at 34 g/day reduces the number of hospitalizations due to the complications of alcoholic liver cirrhosis such as infection, gastrointestinal bleeding, ascites, and hepatic encephalopathy.[265] Depending on the state of the patient, protein and calorific intakes of 1.2-1.5 g/kg/day protein and 35-40 kcal/kg/day, respectively, are recommended.[266] If three meals per day does not provide an adequate nutritional intake, a greater number of smaller meals is recommended.[267-269] If the patient is actively ill or in a critical state, higher protein (1.5 g/kg/day) and calorific (40 kcal/kg/day) intakes should be considered in conjunction with medical treatment.

While long term oral or parenteral nutrition is thought to be helpful for patients with alcoholic liver cirrhosis, definite conclusions cannot be drawn at present due to limitations in previous studies such as small sample size or insufficient treatment periods.[260] Sufficient nutritional support can reduce the complications of ALD without imposing any additional risk.[270]

Currently there are no clear guidelines regarding the supplementation of vitamins or minerals in patients with ALD. However, it is recommended that patients with nutritional deficiency should be given adequate amounts of vitamin A, thiamine, vitamin B12, folic acid, pyridoxine, vitamin D, and zinc along with nutritional therapy.[270,271]

[Recommendations]

18. Active and sufficient nutritional support should be provided to patients with ALD. If three meals per day do not provide adequate nutrition, additional meals in the early morning and late at night can help restore nutritional balance. (B1)

19. Vitamin and mineral supplementation should be provided along with nutritional therapy to patients with ALD. (B1)

TREATMENT OF ALCOHOLIC HEPATITIS

Alcohol abstinence

Alcohol abstinence is the most important treatment for alcoholic hepatitis,[57] and should be administered as described above.

Nutritional therapy

Most patients with severe alcoholic hepatitis are malnourished. Although several studies have shown that enteral nutrition improves the survival rate irrespective of steroid treatment, it is still not clear whether nutritional therapy is effective in treating severe alcoholic hepatitis.[263,272]

Steroids

Corticosteroids (prednisolone 40 mg/day for 28 days) are the most commonly recommended treatment for severe alcoholic hepatitis. They are thought to act by reducing the transcription of pro-inflammatory cytokines such as TNF-α. In patients with histologically confirmed severe alcoholic hepatitis, serum levels of TNF-α and intercellular adhesion molecule-1 (ICAM-1) were shown to decrease with steroid treatment, and the degree of change in the soluble form of ICAM-1 was found to be correlated with the degree of histological improvement.[273]

Indications for treatment with steroids are the presence of severe alcoholic hepatitis with a poor prognosis. Various prognosis prediction models such as mDF, MELD, and GAHS can be used to determine which patients should take steroids. Scores of mDF score ≥32, MELD >21, or GAHS ≥9, or hepatic encephalopathy are commonly used indications. Steroids are usually contraindicated in those with gastrointestinal bleeding, renal failure, pancreatitis, or uncontrolled infection.

Steroid treatment for alcoholic hepatitis has been investigated in many randomized controlled trials, and conflicting results were obtained in early clinical studies and meta-analyses.[55,210,274-278] While a Cochrane review of 15 studies found no survival benefit from steroids,[278] a subgroup analysis involving only "low-bias risk" studies revealed a survival benefit from steroids in patients with an mDF score of ≥32 or with hepatic encephalopathy.[278] An analysis involving pooled data found that the 28-day survival rate was higher in the steroid group (84.6%) than in the placebo group (65.1%; $P=0.001$).[277] That finding was recently confirmed in a study using data from the five recent randomized controlled trials

(28-day survival rate: treatment group, 80.0%; placebo group, 65.7%; P=0.0005).[210] Therefore, steroids should be useful in patients with an mDF score of ≥32.

ECBL and the Lille model were recently introduced to predict prognosis based on the response to steroid treatment (Table 5). ECBL is defined when the bilirubin level at 7 days of treatment is lower than that on the first day of treatment. One study found that the 6-month survival rate was 82% in severe alcoholic hepatitis patients with confirmed ECBL but only 23% in those without ECBL.[224] The Lille model is an improved model that includes ECBL as well as several additional variables. The probability of death is scored from 0 to 1 in the Lille model, and the 6-month survival rate was 25% in those patients with a score of >0.45, which is significantly lower than that of 85% for those with a Lille score of <0.45.[226] In a more recent study, patients were subdivided according to the percentile distribution of the Lille scores (≤35th, 35th-70th, and ≥70th percentiles), and classified as complete responders (≤0.16), partial responders (0.16-0.56), and null responders (≥0.56); the 28-day survival rate differed significantly between these groups, at 91.1%, 79.4%, and 53.3%, respectively.[210] Given that infection occurs more frequently in patients who do not re-spond to steroid treatment than in those who do respond, it would be reasonable to discontinue steroids if the patient is thought to be a null responder based on ECBL or the Lille model.[279] The survival rate in these patients may be significantly higher after liver transplantation than when continuing with medical treatment only.[280] However, a social consensus is needed on this issue.

In conclusion, treatment with steroids is effective in patients with mDF scores of ≥32. However, if ECBL is not observed or the Lille score is ≥0.56, steroids should be discontinued and other rescue therapies such as liver transplantation should be considered (Fig. 3).[210,224,226]

Pentoxifylline

Pentoxifylline, given at a dose of 400 mg three times daily for 28 days, may be tried as an alternative to steroids for treating severe alcoholic hepatitis.[281] Pentoxifylline is a selective phosphodiesterase inhibitor that increases intracellular cAMP levels, which in turn decrease the expression of cytokines such as TNF-α, IL-8, and macrophage inflammatory protein-1a.[282] Pentoxifylline may be
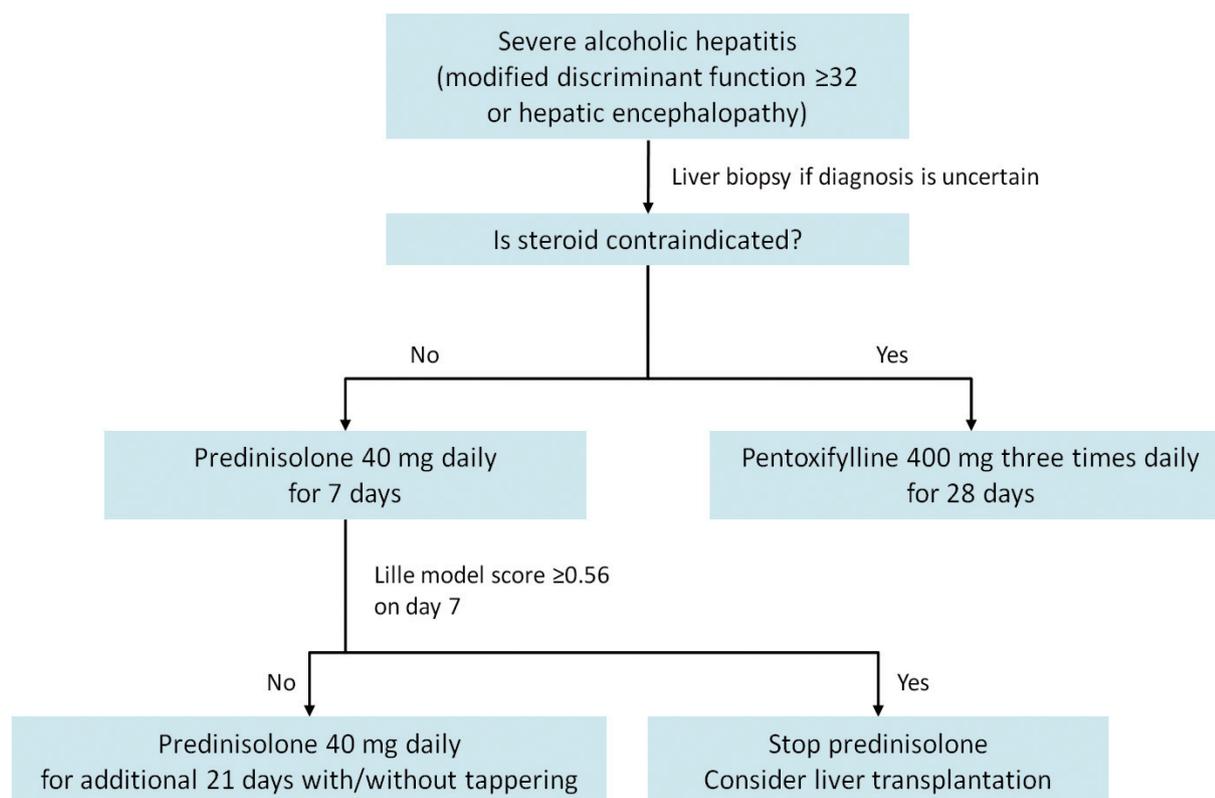

Figure 3. Treatment algorithm for severe alcoholic hepatitis.

used in patients with infection or renal failure. A study involving 101 patients with severe alcoholic hepatitis found that the 28-day mortality rate was significantly lower in the pentoxifylline group (24.5%) than in the placebo group (46.1%).[281] Given that the percentage of deaths due to hepatorenal syndrome was 50% (6 of 12 patients) in the pentoxifylline group and 92% (22 of 24 patients) in the placebo group, it appears that the increase in survival rate may be due to a decrease in the incidence of hepatorenal syndrome.[281]

A randomized comparative study of pentoxifylline and steroids found that the death rate was lower in the pentoxifylline group.[283] However, that study involved only a small group of patients, and the survival rate in the steroid group was far lower than that reported previously, thereby questioning the validity and acceptability of the conclusion. Another randomized controlled trial comparing the efficacies of pentoxifylline and corticosteroids in treating severe alcoholic hepatitis was recently performed in Korea. The 1-month survival rate of patients receiving pentoxifylline was 74.5%, compared to 87.0% in those receiving prednisolone. Although the trial was intended to assess the non-inferiority of pentoxifylline compared to corticosteroids, the observed efficacy of pentoxifylline was not statistically equivalent to that of corticosteroids, supporting corticosteroids as a preferred option for severe alcoholic hepatitis.[284]

It is currently unclear whether combination therapy of steroids and pentoxifylline is superior to monotherapy with either agent. A recent study found no survival benefit at 4 weeks or 6 months with combination therapy of steroids and pentoxifylline.[285] Therefore, combination therapy is not recommended at present.

The efficacy of early switching to pentoxifylline in steroid non-responders has been investigated by either switching patients without ECBL to pentoxifylline or continuing them on steroids;[286] the 2-month survival rates did not differ between the two groups, at 35.5% and 31.0%, respectively. Pentoxifylline is therefore not recommended as a rescue therapy since steroid non-responders do not seem to obtain any benefit from an early switch to this drug.

In spite of these limitations, pentoxifylline is considered an effective alternative agent to steroids in the treatment of severe alcoholic hepatitis and improves survival rate.[287]

Anti-TNF-α agents

Several anti-TNF-α agents have been tested as treatments for alcoholic hepatitis under the assumption that clinical improvement may be seen by blocking TNF-α, a major cytokine involved in alco-

holic hepatitis. A pilot study demonstrated the efficacy of combination therapy of infliximab and steroids.[288] However, the mortality rate was found to be higher with combination therapy in a follow-up study, and therefore infliximab is currently not recommended for the treatment of severe alcoholic hepatitis.[289] Treatment with etanercept was also associated with a higher 6-month mortality rate, mainly due to higher rates of serious infections compared to the placebo group.[290] Therefore, anti-TNF-α agents are currently not recommended for the treatment of alcoholic hepatitis.

Antioxidants

N-acetylcysteine has not yet been found to be effective as a treatment for alcoholic hepatitis.[291] A recent trial of combination therapy with *N*-acetylcysteine and steroids found an increase in the short-term survival rate but no improvement in the long-term survival rate.[292] Specifically, the 1-month mortality rate was lower in the combination therapy group (8%) than in the steroid-only group (24%), but the 3-month and 6-month survival rates did not differ significantly between the two groups. Interestingly, the number of deaths due to hepatorenal syndrome was lower in the combination therapy group (9%) than in the steroid-only group (22%).[292] Further research is needed to evaluate the efficacy of *N*-acetylcysteine.

[Recommendations]

20. Alcohol abstinence is the single most important treatment for improving survival in alcoholic hepatitis. (A1)

21. Treatment with steroids is needed for patients with severe alcoholic hepatitis who have an mDF score of ≥32. (A1)

22. During steroid treatment it is important to identify patients with a high mortality risk based on ECBL or the Lille score, where rescue therapy such as liver transplantation may be considered. (B1)

23. Pentoxifylline is an alternative treatment agent to steroids that can improve the survival rate in patients with severe alcoholic hepatitis. (B1)

Future research

1. There is a need for new drugs that may be combined with steroids or pentoxifylline to increase the therapeutic efficacy in the treatment of severe alcoholic hepatitis.

2. There is a need to identify clinical factors that respond to ste-

roids or pentoxifylline in the treatment of severe alcoholic hepatitis.

LIVER TRANSPLANTATION

ALD is one of the most common indications for liver transplantation in North America and Europe.[293,294] There is a tendency to avoid liver transplantation in chronic drinkers due to concerns about their continued drinking damaging the transplanted liver. The survival rate of livers transplanted due to ALD is similar to[295-298] or higher than[293] that of liver transplantation due to other causes. Indications for transplantation in ALD are identical to those in other end-stage liver diseases. It is also known that the presence of ALD has no impact on the survival rate following liver transplantation in those with end-stage liver disease.[299]

The increase in survival rate following liver transplantation is limited to CTP class C patients with decompensated liver cirrhosis.[300,301] The 1-year and 5-year survival rates were found to be increased in CTP class C patients after liver transplantation than in the control group, but no such statistically significant increase in survival rate was seen in CTP class A or B patients.[300]

Six months of alcohol abstinence may result in improvement of liver disease and avoid unnecessary liver transplantation; therefore, an abstinence period of 6 months prior to liver transplantation is thought to be necessary.[298,302-306] However, many recent studies have questioned whether 6 months of abstinence is a reliable predictor for resumption of drinking following transplantation, and have found poor predictability.[307,308]

Recidivism following liver transplantation is common, with estimated rates of 10-52%.[295,296,298,304-306,308-315] Alcohol consumption following liver transplantation causes histologic damage in the liver, including liver fibrosis.[297,314,316] Heavy drinking following liver transplantation adversely affects the survival rate regardless of the reason for liver transplantation.[304,309,313] Various physical and psychological factors should be carefully evaluated prior to liver transplantation and such factors should also be followed up and monitored following liver transplantation.[317]

For liver transplantation performed in a patient with alcoholic hepatitis alone or alcoholic hepatitis superimposed on alcoholic cirrhosis, the survival rates of the transplanted liver and the patient did not differ significantly from those for patients with alcoholic cirrhosis alone.[298,318,319] Most European and North American liver transplantation centers do not consider patients with severe alcoholic hepatitis as candidates for liver transplantation, based on them not fulfilling the criterion of alcoholic abstinence for 6 months prior to liver transplantation.[46,302] However, a prospective, multicenter study found an increase in survival rate with liver transplantation in patients with severe alcoholic hepatitis who are not responsive to medical treatment.[280] Therefore, liver transplantation may be considered in patients whose severe alcoholic hepatitis has not responded to medical treatment. However, improvement in long term survival must be verified in future studies.

Similar to those who have received liver transplantation for other causes, patients who have received liver transplantation due to ALD exhibit a high incidence of de novo cancer in other areas of the body.[293,295,301,320-322] Such de novo cancers are associated with an increased mortality following transplantation. It is thought that the immunosuppressive drugs that are used post-transplantation are related to the onset of new cancers. It is also known that liver transplantation due to ALD, compared to other causes, is associated with a strikingly high rate of cardiovascular complications.[293]

[Recommendations]

24. Liver transplantation should be considered in patients with decompensated liver cirrhosis. (A1)

25. Early liver transplantation may be considered in patients with severe alcoholic hepatitis who do not respond to medical treatment. (A2)

Future research

1. There is a need to determine the appropriate timeline for liver transplantation with regard to abstinence from alcohol in patients with ALD.

MISCELLANEOUS THERAPIES

Propylthiouracil

Histologic findings of central hypoxia due to thyroid hormone can occur in ALD, raising the question of whether propylthiouracil (PTU) would be effective in reducing pericentral hypoxia and cellular damage by suppressing metabolic activation due to ethanol. Some studies have found that PTU improves the mortality rate by suppressing hypermetabolic activation.[323,324] However, a Cochrane meta-analysis of 6 studies involving 710 ALD patients that compared PTU versus placebo found no clear improvement in liver histology or in the liver-related or overall mortality rate.[325,326]

Colchicine

Colchicine affects liver fibrosis by suppressing collagen production, activating collagenase activity, and suppressing collagen transcellular trafficking. It has also been found to contribute to the production of cytokines that stimulate fibroblast proliferation. As such, colchicine has been investigated as a treatment agent for ALD. Clinical studies involving patients with alcoholic liver cirrhosis found that colchicine exhibited anti-inflammatory and anti-fibrotic effects,[327,328] and had a positive effect on survival.[329] However, subsequent controlled trials produced conflicting results, and a meta-analysis of 15 randomized trials involving 1,714 patients with ALD found no clear association between colchicine and liver function or histologic improvement, or liver-related or overall mortality.[330] Therefore, considering its side effects, colchicine is not recommended for treatment of ALD.

Polyunsaturated lecithin

Polyunsaturated lecithin (PUL) is a cell membrane component found in soybean extract. While its mechanism of action is unclear, it is thought to act by modulating collagenase activity.[331] A study involving baboons with alcoholic liver damage found that PUL caused histologic improvement in the liver and decreased the activation of hepatic stellate cells.[332] However, there was no clear association between polyenylphosphatidylcholine and progression of liver fibrosis in a follow-up randomized controlled study.[333] Since PUL is a component of normal cells with a favorable side effect profile, this agent should be investigated further.

S-adenosyl-L-methionine

SAMe is a methyl-group donor that is involved in the biosynthesis of glutathione, a major intracellular antioxidant. A clinical study found that SAMe improved survival in both CTP class A and B patients compared to the placebo group. Although some studies have found that SAMe has treatment value in ALD, a meta-analysis found SAMe to exert no statistically significant effects on overall mortality,[334,335] liver-related mortality, complications, or liver transplantation results.[336,337]

Metadoxine

Metadoxine antioxidant therapy has been approved for the treatment of ALD in several countries. A large randomized controlled trial involving 136 patients with fatty liver that compared a 3-month course of metadoxine (1,500 mg/day) with placebo found meaningful improvements in liver function in both groups but with a faster recovery course in the metadoxine group.[338] The persistence of fatty liver as visualized by ultrasonography was significantly decreased in the metadoxine group relative to the placebo group (28% vs. 70%). These positive effects were more noticeable in patients who had abstained from alcohol than in those who had continued to drink. However, the clinical implications remain unclear, and metadoxine is therefore not recommended for the treatment of ALD. Further research is needed to investigate the effects of metadoxine.

Angiotensin II receptor blocker

One randomized controlled trial has found that combination therapy with the angiotensin II receptor antagonist candesartan and ursodeoxycholic acid effects a greater histologic improvement than monotherapy with ursodeoxycholic acid.[339]

Anti-cytokine agents

Anti-cytokine treatment has been proposed based on the effect of cytokines on liver fibrosis and cirrhosis.[340] Although there are reports of anti-inflammatory effects of thalidomide, misoprostol, adiponectin, and probiotic agents, more evidence is needed before these agents should be used as treatments for ALD.[341-343]

Silymarin

Silymarin, a milk thistle extract with activating and anti-oxidative properties, has been evaluated in many studies as a potential treatment agent for ALD.[344,345] Although one study found that silymarin contributes to improved survival, this result has not been confirmed for ALD patients in meta-analyses such as the Cochrane review.[344,346]

Future research

1. There are isolated reports that PTU, colchicine, PUL, SAMe, metadoxine, and silymarin affect the prognosis of ALD patients, but these have not been confirmed. There is a need to investigate new pharmacologic agents.

STRATEGIES FOR THE REDUCTION AND PREVENTION OF HARMFUL USE OF ALCOHOL

Chronic, excessive alcohol consumption and binge drinking are risk factors for various physical and psychological diseases; there should thus be consistent and nationwide efforts to address this issue. Strategies for decreasing the harmful use of alcohol should be implemented through various public, private, and government organizations.[347] In 2010 the WHO implemented the "Global Strategy to Reduce Harmful Use of Alcohol" campaign and proposed areas for national action.[348] However, the lenient culture toward drinking, cheap pricing of distilled beverages, and easy accessibility to alcohol in Korea have all contributed to the physical, psychological, social, and economical damage caused by alcohol use.[349]

Strategies to reduce the harmful use of alcohol include reducing its accessibility by limiting sales or increasing prices, restricting alcohol-related advertising, promoting preventive education and public campaigns, and implementing early identification and intervention programs. Verified strategies such as increasing prices and limiting accessibility are currently not in place in Korea, and the adolescent-related policies that are present are not strictly enforced. Furthermore, preventive education and public campaigns are grossly insufficient due to issues such as budgetary constraints, and early identification and intervention programs for hazardous or harmful drinking are not being implemented appropriately at present. There is a need for a change in the public perception toward harmful use of alcohol and specific and realistic strategies for alcohol control such as enforcing the legal drinking age, restricting alcohol-related advertisements, modifying liquor taxes, setting minimum prices for alcohol, limiting public drinking, and starting early intervention and mandatory treatment programs for intoxicated individuals.[347,350]

[Recommendation]

26. There is a need to increase public attention towards the harmful use of alcohol, and specific strategies such as limiting the accessibility of alcohol, price controls, and banning alcohol-related advertisements should be implemented. (A1)

Acknowledgements

Conflicts of Interest

The authors have no conflicts to disclose.

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Appendix 1. Definition of alcohol use disorder (AUD), as suggested by the fifth edition of the diagnostic and statistical manual of mental disorders (DSM-V) of the American psychiatric association

A.		A problematic pattern of alcohol use leading to clinically significant impairment or distress.
B.		Two (or more) of the following occurring within a 12-month period:
	1	Alcohol is often taken in larger amounts or over a longer period than was intended
	2	There is a persistent desire or unsuccessful effort to cut down or control alcohol use
	3	A great deal of time is spent in activities necessary to obtain alcohol, use the substance, or recover from its effects
	4	Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
	5	Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance
	6	Important social, occupational, or recreational activities are given up or reduced because of alcohol use
	7	Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
	8	Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
	9	Tolerance, as defined by either or both of the following:
	a	A need for markedly increased amounts of alcohol to achieve intoxication or desired effect
	b	Markedly diminished effect with continued use of the same amount of the substance
	10	Withdrawal, as manifested by either of the following:
	a	The characteristic withdrawal syndrome for alcohol (refer to criteria A and B of the criteria set for withdrawal)
	b	The same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms
	11	Craving or a strong desire or urge to use alcohol

The AUD severity is defined as follows: no or 1 criterion, no diagnosis; 2 or 3 criteria, mild AUD; 4 or 5 criteria, moderate AUD; ≥6 criteria, severe AUD.

Appendix 2. The CAGE (cut down, annoyed, guilt, eye-opener) questionnaire

Have you ever felt you should cut down on your drinking?
Have people annoyed you by criticizing your drinking?
Have you ever felt bad or guilty about your drinking?
Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (eye-opener)

Two or more "yes" responses indicate an alcohol use disorder.

Appendix 3. The alcohol use disorders identification test (AUDIT)

		0	1	2	3	4
1	How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
2	How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 or 9	10 or more
3	How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4	How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5	How often during the last year have you failed to do what was normally expected from you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6	How often during the last year have you needed a drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7	How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8	How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9	Have you or someone else been injured as a result of your drinking?	No		Yes, but no in the last year		Yes, during the last year
10	Has a relative, friend, or healthcare provider been concerned about your drinking or suggested you cut down?	No		Yes, but no in the last year		Yes, during the last year

AUDIT can detect alcohol-related problems experienced in the past year. A score of 8+ on AUDIT generally indicates harmful or hazardous drinking. Questions 1–8 receive a score of 0, 1, 2, 3, or 4. Questions 9 and 10 receive a score of 0, 2, or 4 only.

Appendix 4. Alcohol use disorders identification test – K (AUDIT-K)

		0	1	2	3	4
1	얼마나 자주 술을 마십니까?	안마심	월 1회 이하	월 2-4회	주 2-3회	주 4회 이상
2	술을 마시면 한번에 몇 잔 정도 마십니까?	소주 1-2잔	소주 3-4잔	소주 5-6잔	소주 7-9잔	소주 10잔 이상
3	한번에 소주 1병 또는 맥주 4병 이상 마시는 경우는 얼마나 자주 있습니까?	없다	월 1회 미만	월 1회	매주	거의 매일
4	지난 일년간 한번 술을 마시기 시작하면 멈출 수 없었던 때가 얼마나 자주 있었습니까?	없다	월 1회 미만	월 1회	매주	거의 매일
5	지난 일년간 평소 같으면 할 수 있던 일을 음주 때문에 실패한 적이 얼마나 자주 있었습니까?	없다	월 1회 미만	월 1회	매주	거의 매일
6	지난 일년간 술을 마신 다음날 일어나기 위해 해장술이 필요했던 적은 얼마나 자주 있었습니까?	없다	월 1회 미만	월 1회	매주	거의 매일
7	지난 일년간 음주 후에 죄책감이 든 적이 얼마나 자주 있었습니까?	없다	월 1회 미만	월 1회	매주	거의 매일
8	지난 일년간 음주 때문에 전날 밤에 있었던 일이 기억나지 않았던 적이 얼마나 자주 있었습니까?	없다	월 1회 미만	월 1회	매주	거의 매일
9	음주로 인해 자신이나 다른 사람이 다친 적이 있습니까?	없다		있지만, 지난 1년간 없음		지난 1년간 있음
10	친척이나 친구, 의사가 당신이 술 마시는 것을 걱정하거나 당신에게 술 끊기를 권유한 적이 있었습니까?	없다		있지만, 지난 1년간 없음		지난 1년간 있음

AUDIT-C: 얼마나 자주 술을 마십니까? 술을 마시면 한번에 몇 잔 정도 마십니까? 한번에 소주 1병 또는 맥주 4병 이상 마시는 경우는 얼마나 자주 있습니까?
적정음주자: 남성, 9점 이하; 여성 5점 이하.
위험음주자: 남성 10-19점; 여성, 6-9 점.
알코올사용장애 추정자: 남성, 20점 이상; 여성, 10점 이상.