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TOPIC HIGHLIGHT

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Clinical differences between alcoholic liver disease and nonalcoholic fatty liver disease

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Abstract

Alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) are serious health problems worldwide. These two diseases have similar pathological spectra, ranging from simple hepatic steatosis to steatohepatitis, liver cirrhosis, and hepatocellular carcinoma. Although most subjects with excessive alcohol or food intake experience simple hepatic steatosis, a small percentage of individuals will develop progressive liver disease. Notably, both ALD and NAFLD are frequently accompanied by extrahepatic complications, including cardiovascular disease and malignancy. The survival of patients with ALD and NAFLD depends on various disease-associated conditions. This review delineates the clinical characteristics and outcomes of patients with ALD and NAFLD by comparing their epidemiology, the factors associated with disease susceptibility and progression, and the predictors and characteristics of outcomes. A comprehensive understanding of the characteristics and outcomes of ALD and NAFLD is imperative in the management of these chronic liver diseases.

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Key words: Alcoholic liver disease; Nonalcoholic fatty liver disease; Clinical characteristics; Outcomes; Chronic liver disease

Core tip: Although alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) have similar pathological spectra, from simple hepatic steatosis to steatohepatitis and liver cirrhosis, the epidemiological and clinical characteristics of these two diseases differ. Comparative analyses of the factors associated with disease susceptibility and progression and the predictors and characteristics of outcomes would be helpful in the management of these diseases. Notably, both ALD and NAFLD are frequently accompanied by extrahepatic complications, including cardiovascular disease and malignancy, which can influence patient survival.

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INTRODUCTION

Excessive alcohol intake is associated with various diseases, including alcoholic liver disease (ALD), cardiovascular disease, and cancer[1]. The prevalence of alcohol use disorders increased dramatically in the sixteenth century when alcohol distillation became more widespread, and alcohol-associated diseases have continued to afflict humanity[2]. A recent review reported that alcohol substantially contributes to the global burden of disease and is responsible for 4.6% of disability-adjusted life-years and 3.8% of all deaths[1]. Moreover, alcohol has a negative effect on socioeconomic activities; the cost of excessive social drinking is 1% or more of the gross domestic

product in high-income countries[3].

Excessive food intake can lead to overweight and obesity. An estimated 1.46 billion adults worldwide had a body mass index (BMI) of 25 kg/m^2 or higher in 2008, which reflects modern overnutrition[4]. Metabolic syndrome often develops in obese individuals, and nonalcoholic fatty liver disease (NAFLD) has been recognized as the liver manifestation of metabolic syndrome[5]. A recent study from the United States found that the annual healthcare costs were 1.6-fold higher for subjects with metabolic syndrome than for those without metabolic syndrome[6].

ALD and NAFLD are both serious health and socioeconomic problems worldwide. Although these diseases have similar pathological spectra, ranging from simple hepatic steatosis to steatohepatitis and liver cirrhosis[7], ALD and NAFLD differ from each other in many characteristics, ranging from differences in clinical features to patient outcomes. A comparison of these diseases may result in a better understanding and management of both ALD and NAFLD. Therefore, in this review, we comprehensively characterized ALD by comparing its clinical features and outcomes with those of NAFLD.

EPIDEMIOLOGY

Table 1 displays the epidemiology of ALD and NAFLD. Comprehensive data regarding the prevalence of ALD are scarce. Geographic differences in alcohol intake have been reported. For example, Eastern Europe has the highest annual per capita intake (15.7 L per person), while North Africa and the Middle East have the lowest (1.0 L per person)[8]. Although patterns of alcohol intake may affect the prevalence of ALD, studies from Europe, the United States, and Asia, in which hepatic steatosis was assessed using ultrasonography or magnetic resonance imaging, reported that the prevalence of NAFLD ranged from 12.9% to 46.0%[9-12]. A study from Japan demonstrated that the prevalence of NAFLD had increased over time from 12.6% in 1989 to 28.4% in 2000[13]. Moreover, a recent study from China, where the per capita annual alcohol intake is 4-6 L per person[8], found that the prevalence rates of ALD and NAFLD were 4.5% and 15.0%, respectively, and both rates are expected to increase in the future[14].

Age

A study from the United States revealed that the peak prevalence of hospitalization for alcohol-related conditions was between 45 and 69 years of age[15]. In contrast, the prevalence of NAFLD in a large Japanese study peaked at 40-49 years of age in males and at age 60-69 years in females[12]; however, a large study in China found that the prevalence of NAFLD in both males and females peaked at 60-69 years of age[16]. In addition, NAFLD is commonly observed in children; a recent autopsy study from the United States revealed that approximately 10% of children had NAFLD[17].

Gender

ALD is predominantly observed in males. For example, a cross-sectional study revealed that the male to female ratio of patients with alcoholic liver cirrhosis was 9:1[18]. A nationwide study in the United States that assessed patients discharged from the hospital following a diagnosis of ALD found that 4.5 per 100000 persons had acute alcoholic hepatitis, with a male to female ratio of 1.83:1, and that 13.7 per 100000 persons had chronic alcoholic hepatitis with cirrhosis, with a male to female ratio of 2.64:1[19]. Studies have also revealed a male predominance in the prevalence of NAFLD. For example, a study from the United States found that 58.9% of patients with NAFLD were male[11], and a large study from Japan reported that the prevalence rates of NAFLD in males and females were 41.0% and 17.7%, respectively. The prevalence rates of NAFLD were higher at all ages in males than in females, but the rate gradually increased in females with age, from 3.3% in the second decade of life to 31.3% beyond the sixth decade[12]. Similar trends were observed in the Chinese population[20].

Ethnicity

Studies have reported ethnic differences in the prevalence rates of ALD and NAFLD. For example, the prevalence rate of alcoholic liver cirrhosis was higher among South Asian males (32.8%) than among Afro-Caribbean males (1.1%) in the United Kingdom[21]. A recent large study of patients with NAFLD indicated that the prevalence of this disease was higher in Hispanics (24.2%) than in non-Hispanic Whites (17.8%) and non-Hispanic Blacks (13.5%)[22].

DIAGNOSTIC PROCEDURES

Differentiation

As mentioned above, ALD and NAFLD have similar pathological spectra, from simple steatosis to liver cirrhosis, which makes confident differentiation of the two diseases difficult. However, the following histological findings are helpful in the differential diagnosis[7]. The fatty degeneration of liver cells occurs to a greater degree in NAFLD than in ALD. In contrast, inflammatory cell infiltration is more pronounced in ALD than in NAFLD. Furthermore, venous or perivenular fibrosis, phlebosclerosis, and (less commonly) lymphocytic phlebitis are more common in ALD than in NAFLD.

Clinically, the differentiation between ALD and NAFLD is usually performed by taking a history of a patient's alcohol intake combined with laboratory and imaging examinations; however, the reliability of these methods may not be high[23]. Therefore, discriminant indices consisting of clinical parameters have been developed[24-26]. For example, the ALD/NAFLD index (ANI) is calculated from a patient's gender, BMI, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, and mean corpuscular volume (MCV)[25]. This index has exhibited a high diagnostic accuracy, with an area un-

Table 1 Epidemiology of alcoholic liver disease and nonalcoholic fatty liver disease

	ALD	NAFLD	Ref.
Prevalence rate (overall)	Unclear (rates may reflect geographical differences in the amount of alcohol intake)	12.9%-46.0%	[8-12]
Prevalence rate (China)	4.50%	15.0%	[14]
Trend (Japan)		Increasing (12.6% in 1989; 28.4% in 2000)	[8]
Peak age	45-69 yr (United States)	40-49 yr in males; 60-69 yr in females (Japan)	[12,15]
		60-69 yr (China)	[16]
Gender	Male dominant	Male dominant	[11,12,18-20]
Ethnicity	South American males > Afro-Caribbean males	Hispanics > Whites > Blacks	[21,22]

ALD: Alcoholic liver disease; NAFLD: Nonalcoholic fatty liver disease.

der the receiver operating characteristic curve (AUROC) of 0.983 (cut-off value, 0; sensitivity, 93.5%; specificity, 92.0%) in the derivation set and AUROCs of 0.974, 0.989, and 0.767 in the three validation sets. A recent validation study confirmed the high accuracy of the index[27]. However, the ANI may be less reliable in patients with end-stage liver disease because these patients frequently have an elevated MCV and an increased AST/ALT ratio[25]. Because the ANI was formulated based on data sets mainly obtained from Caucasians, this index may not be applicable to other ethnic groups, suggesting the need for indices specifically for these groups.

Assessment of disease stage

Following a differential diagnosis, the assessment of disease severity and stage is vital for optimal patient management. Although a liver biopsy is the gold standard, this procedure is invasive and costly and is accompanied by patient discomfort, which affects its feasibility. Non-invasive methods for assessing the stage of fibrosis have been recently developed, including fibrosis indices and transient elastography[28]. Many fibrosis indices have been devised based on clinical parameters, and the usefulness of these indices has been tested in patients with chronic liver diseases. The AST/platelet ratio index (APRI)[29], the FIB-4 index[30], and the FibroTest[31] have been validated for use in assessing the fibrosis stage in patients with both ALD and NAFLD. The AUROC of the FibroTest for the diagnosis of liver cirrhosis in patients with ALD was 0.95 (cut-off value, 0.7; sensitivity, 91%; specificity, 87%)[32], while a more recent study found that the AUROCs of the APRI, the FIB-4 index, and the FibroTest for liver cirrhosis in patients with ALD were 0.67, 0.80, and 0.94 (cut-off value, 0.7; sensitivity, 86.6%; specificity, 86.0%), respectively[33]. In patients with NAFLD, the AUROCs of the APRI and the FIB-4 index for the diagnosis of advanced fibrosis were 0.73 and 0.80 (cut-off value, 2.67; sensitivity, 33%; specificity, 98%), respectively[34], and in another study, the AUROCs for the APRI and the FIB-4 index were 0.82 (cut-off value, 1; sensitivity, 67%; specificity, 81%) and 0.87 (cut-off value, 3.25; sensitivity, 48%; specificity, 95%), respectively[35]. Another study in patients with NAFLD indicated that the AUROCs of the FibroTest for the diagnosis of advanced fibrosis in two independent cohorts were 0.92 (cut-off value, 0.7; sensitivity, 25%; specificity, 97%) and 0.81(cut-off value, 0.7; sensitivity, 25%; specificity, 99%), respectively[36].

Transient elastography has also been shown to be useful in assessing the disease stage. For example, the accuracy of this method in assessing the fibrosis stage was validated for ALD, with AUROCs of 0.94 (cut-off value, 11.60 kPa; sensitivity, 87%; specificity, 89%) for advanced fibrosis and 0.87 (cut-off value, 22.70 kPa; sensitivity, 84%; specificity, 83%) for liver cirrhosis[37]. The AUROCs of transient elastography, the APRI, and the FIB-4 index for the diagnosis of advanced fibrosis in patients with NAFLD were 0.93 (cut-off value, 9.6 kPa; sensitivity, 63.6%; specificity, 83.7%), 0.74 (cut-off value, 0.5; sensitivity, 65.1%; specificity, 72.3%), and 0.80 (cut-off value, 2.67; sensitivity, 20.6%; specificity, 95.5%), respectively[38]. Generally, transient elastography cannot differentiate simple hepatic steatosis from mild hepatic fibrosis but can assess the degree of hepatic fibrosis.

Recently, a novel measurement method for assessing the hepatic steatosis grade was developed, which has been designated as the controlled attenuation parameter (CAP)[39]. This method is based on transient elastography and permits a simultaneous evaluation of the fibrosis stage and the steatosis grade. Studies have demonstrated the usefulness of CAP in quantitatively assessing the steatosis grade with a high accuracy[40-42]. A large cohort study found that the AUROCs of the CAP for the diagnosis of steatosis > 10%, steatosis > 33%, and steatosis > 66% were 0.79, 0.84, and 0.84, respectively, in 440 patients who underwent a liver biopsy[42]. This study also found that elevated CAP values were significantly associated with excessive alcohol intake, indicating a possible clinical application of CAP in the diagnosis and management of ALD.

Further validation studies are required to establish the usefulness of these non-invasive methods in patients with ALD and NAFLD.

Scoring systems for ALD and NAFLD

Scoring systems specific for ALD or NAFLD have been developed to assess disease severity and stage

Table 2 Rates of alcoholic liver disease and nonalcoholic fatty liver disease progression and the factors associated with susceptibility and progression

	ALD	NAFLD	Ref.
Rate of progression from simple hepatic steatosis to liver cirrhosis	1.0%-3.1% per year	0%-2.5% per year	[51-55]
Rate of progression from steatohepatitis to liver cirrhosis	3.2%-12.2% per year	1.3%-3.5% per year	[51-54]
Environmental factors associated with disease susceptibility	Increased alcohol intake	Increased calorie intake	[18,50,57]
	Daily heavy drinking, not episodic or binge drinking		[18,60]
		Fructose	[62]
Environmental factors associated with disease progression	Increased amount of alcohol intake	Higher intake of soft drinks and meats	[58,61]
	Spirits rather than beer or wine	Fructose	[59,62]
Host factors associated with disease susceptibility			
Age	Older age		[65,66]
Gender	Female		[57]
Body mass index	Obesity	Obesity	[22,58,67]
Metabolic syndrome	Presence	Presence	[22,71,72]
Type 2 diabetes	Presence	Presence	[71,72]
Ethnicity	Hispanic, Black	Hispanic	[11,73,74]
Genetic variant	*PNPLA3* rs738409 G	*PNPLA3* rs738409 G	[80-84]
Host factors associated with disease progression			
Age	Older age	Older age	[58,67,68]
Gender	Female	No difference	[52,55,58,67]
Body mass index	Obesity		[58,67]
Metabolic syndrome			
Type 2 diabetes			
Ethnicity			
Genetic variant	*PNPLA3* rs738409 G	*PNPLA3* rs738409 G	[80-84]

ALD: Alcoholic liver disease; NAFLD: Nonalcoholic fatty liver disease.

and/or to predict patient outcomes. Scoring systems for ALD[43,44] include Maddrey's discriminant function (mDF), the glasgow alcoholic hepatitis score (GAHS), the Age-Bilirubin-international normalized ratio (INR)-Creatinine (ABIC) score, and the Lille score. Studies have demonstrated that these systems are useful in predicting the short-term survival of patients with alcoholic hepatitis[44,45]. The Brunt score[46] and the NAFLD activity score (NAS)[47] are histological scoring systems for NAFLD. Studies have suggested that the NAS has an excellent ability to differentiate simple hepatic steatosis from nonalcoholic steatohepatitis (NASH)[48]. Other scoring systems for the assessment of NAFLD stage, such as the NAFLD fibrosis score and the BARD score, have shown promising results[49].

FACTORS ASSOCIATED WITH DISEASE SUSCEPTIBILITY AND PROGRESSION

Simple hepatic steatosis occurs in most subjects who ingest excessive amounts of alcohol[2] or food[50]. However, only a small percentage of these individuals will develop advanced liver fibrosis or liver cirrhosis. Repeat liver biopsies at 4-year intervals in patients with ALD indicated that liver cirrhosis developed in 11% of the patients with simple hepatic steatosis and 39% of those with alcoholic hepatitis[51]. A recent cohort study of patients with ALD estimated that the 5-year risk of cirrhosis was 6.9% for patients with simple hepatic steatosis and 16.0% for patients with steatohepatitis[52]. Studies examining the histological course of NAFLD over a mean follow-up period of 3.2-13.8 years found that liver cirrhosis developed in 0%-8% of the patients without hepatic fibrosis and 11.3%-17.6% of those with hepatic fibrosis[53,54]. A long-term (approximately 20 years) follow-up study on simple hepatic steatosis observed that 22% of patients with ALD and 1.2% of those with NAFLD developed liver cirrhosis[55]. A recent autopsy study found that the ratios of simple hepatic steatosis to steatohepatitis or liver cirrhosis were 2.33:1 in ALD patients and 3.60:1 in NAFLD patients[56]. The differences in disease progression may be caused by environment-host interactions. Table 2 contains the environmental and host factors that have been suggested by clinical and/or basic research. Recent advances in genetics have provided further insight into the host factors that can affect disease progression.

Environmental factors

The risks for the development and progression of ALD are increased as the intake of alcohol increases[18,57,58]. The type of beverage may also modify ALD progression. In a pooled cross-sectional time-series analysis, the consumption of spirits, rather than beer or wine, was associated with mortality from cirrhosis in primarily beer-drinking countries[59]. Drinking patterns are also factors associated with ALD. Studies have demonstrated that daily or

near-daily heavy drinking, not episodic or binge drinking, is closely associated with ALD development[18,60]. Moreover, it was demonstrated that alcohol intake outside of mealtimes and the intake of multiple, different beverages increase the risk of developing ALD[18].

Similarly, a high total energy intake is positively associated with the development of NAFLD[50], and specific dietary components affect the pathogenesis of this disease. A cross-sectional study found that a greater intake of soft drinks and meats was associated with an increased risk of NAFLD[61]. Fructose may contribute to disease progression[62] and disease development[63], whereas the ingestion of n-3 polyunsaturated fatty acids may decrease intrahepatic fat deposition[64].

Host factors

Age: The ability to metabolize alcohol decreases with age because aging causes reductions in liver size and blood flow to the liver and decreases the activity of enzymes related to alcohol metabolism, such as alcohol dehydrogenase, acetaldehyde dehydrogenase, and cytochrome P-4502E1[65,66]. Thus, the livers of older subjects become more vulnerable to alcohol toxicity. Indeed, studies in patients with ALD revealed positive correlations between age and advanced fibrosis or liver cirrhosis[58,67]. Similarly, a systematic review of NASH patients revealed that aging was significantly associated with increased fibrosis[68]. The aging of the human population worldwide will likely have an impact on the progression of ALD and NAFLD.

Gender: Females have been found to be more susceptible to alcohol-induced liver damage than males. For example, a large prospective study found that the amount of alcohol intake at which the relative risk of ALD is greater than 1 was lower in females (7-13 beverages per week) than in males (14-27 beverages per week)[57], and multivariate analyses indicated that female gender was significantly associated with increased fibrosis in patients with ALD[58,67]. Studies of patients with simple alcoholic steatosis found that females were at a higher risk for cirrhosis than males[52,55]. In contrast, although a gender difference was observed in the prevalence of NAFLD, no significant gender difference was observed in the risk of increased fibrosis among patients with NASH[68].

Obesity, metabolic syndrome, and type 2 diabetes: Obesity predisposes the individual to the development of both ALD[58] and NAFLD[22]. Although a higher BMI was significantly associated with increased fibrosis in ALD patients[58,67], obesity was not significantly associated with increased fibrosis in patients with NAFLD[68]. Insulin resistance (IR) is a key factor in the development of metabolic syndrome[69] and is largely responsible for the development of type 2 diabetes. Recent studies have demonstrated the close relationship between ALD and IR[70] and have suggested that metabolic syndrome and type 2 diabetes are associated with the development of ALD[71]. In contrast, IR or metabolic syndrome and type 2 diabetes were found to be highly associated with NAFLD development[22,71,72] but not NAFLD progression[68].

Ethnicity: Ethnicity may influence the pathogenesis of ALD and NAFLD. For example, a large cross-sectional study revealed that, among current drinkers, the activities of the liver enzymes AST and γ-glutamyl transpeptidase (GGT) were likely to be 2-fold higher in black non-Hispanic and Mexican Americans than in white non-Hispanic Americans[73]. Another study suggested that African-Americans were more susceptible to alcohol-induced hepatotoxicity than whites[74]. Although the homeostasis model assessment of insulin resistance (HOMA-IR) was not a significant risk factor for NASH among Latinos (OR = 0.93; 95%CI: 0.85-1.02), the HOMA-IR was significant among non-Latino whites (OR = 1.06; 95%CI: 1.01-1.11), which suggests that ethnicity may modulate the effects of IR on the risk of NASH[75].

Genetic factors: Considerable effort has been expended to identify genetic factors that contribute to the pathogenesis of ALD and NAFLD[76,77]. Close links have been found between single nucleotide polymorphisms (SNPs) in DNA and the susceptibility to and severity of many diseases. The patatin-like phospholipase domain-containing 3 gene, *PNPLA3*, encodes adiponutrin[78], a protein thought to play an important role in lipid metabolism, such as the hydrolysis of triacylglycerols[79]. A recent genome-wide association study (GWAS) of NAFLD suggested that a *PNPLA3* SNP, I148M (rs738409 C/G), is associated with increased hepatic fat content and hepatic inflammation[80]. Moreover, a recent meta-analysis[81] confirmed that this SNP strongly correlates with both hepatic fat content (patients with the GG genotype had 73% more hepatic fat than those with the CC genotype) and disease progression (the pooled ORs of the GG *vs* the CC genotype were 3.25 for having higher necroinflammatory scores and 3.26 for developing fibrosis). Notably, these findings were consistent across ethnic groups. Similar results were obtained in patients with ALD[82-84]. For example, a multivariate analysis revealed that the *PNPLA3* SNP was more frequently found in ALD patients than in controls (OR = 1.54) and that this SNP was the strongest independent predictor of the progression of alcoholic liver cirrhosis (OR = 2.08)[84]. These findings regarding the *PNPLA3* SNP may explain, at least in part, the ethnic differences in the susceptibility to and prevalence rates of ALD and NAFLD. For example, Hispanics have been reported to be more susceptible to ALD[73] and have the highest prevalence rate of NAFLD[11]; this is consistent with the frequency of the *PNPLA3* SNP, which is highest among Hispanics[80].

Recent studies have found other *PNPLA3* SNPs associated with NAFLD[85,86]. A recent GWAS of Japanese NAFLD patients identified rs2896019 and rs381062, SNPs that the investigators suggested are associated with the NAFLD grade and/or stage[86]. Additionally, this GWAS also found *SAMM50* and *PARVB* SNPs, both

Table 3 Outcome predictors in patients with alcoholic liver disease and nonalcoholic fatty liver disease

Outcomes	ALD	NAFLD	Ref.
Hepatocarcinogenesis			
Underlying liver disease			
Compensated cirrhosis	Not identified		[90]
Decompensated cirrhosis	Older age		[91]
Compensated/decompensated cirrhosis	*PNPLA3* rs738409 G	Older age, any alcohol intake	[92-94]
	Not identified	Older age, elevated GGT, high CP score	[96]
Unknown stage		Older age, type 2 diabetes, elevated AST, low PLT	[95]
Hepatic decompensation			
	Persistent alcohol intake		[90]
Mortality (overall)			
Underlying liver disease			
Simple hepatic steatosis	Low ALB, severe steatosis	Low ALB	[55]
Simple hepatic steatosis/steatohepatitis		Older age, type 2 diabetes	[101]
Advanced fibrosis/cirrhosis	Persistent alcohol intake, older age, smoking, low ALB	AST/ALT > 1, older age	[99,100]
Compensated cirrhosis	Persistent alcohol intake		[90]
Decompensated cirrhosis	Older age, alcohol abuse, elevated ALP		[97]
	Older age, persistent alcohol intake, low ALB, high MELD score		[98]
	Older age, poor liver function		[91]
Unknown stage		Metabolic syndrome, older age, smoking, Black	[102]
	Type 2 diabetes, insulin resistance	Type 2 diabetes, insulin resistance	[103]

ALD: Alcoholic liver disease; NAFLD: Nonalcoholic fatty liver disease; ALB: Albumin; ALP: Alkaline phosphatase; MELD: Model for end-stage liver disease; GGT: γ-glutamyl transpeptidase; CP: Child-Pugh; AST: Aspartate aminotransferase; PLT: Platelet; ALT: Alanine aminotransferase.

of which were considered to be involved in the second hit of NAFLD, leading to a shift from simple steatosis to NASH. In contrast, a GWAS of Caucasian NAFLD patients identified *FDFT1* and *COL13A1* SNPs[87]. Another GWAS of Caucasian NAFLD patients identified *NCAN* and *PPP1R3B* SNPs, as well as a *PNPLA3* SNP (rs738409), and demonstrated that these SNPs correlate with hepatic steatosis. Furthermore, it was found that SNPs in the *NCAN*, *GCKR*, *LYPLAL1*, and *PNPLA3* genes correlated with histological lobular inflammation/fibrosis[88]. In addition, accumulated data have suggested that some SNPs, other than the *PNPLA3* SNP, may be associated with the pathogenesis of ALD. A meta-analysis revealed a close relationship between a *TNFA* SNP (rs361525) and ALD[89]. Moreover, several studies have found a higher frequency of the *CD14* -159 C/T SNP in patients with alcoholic cirrhosis than in those without this disease[76]. Despite extensive genome-wide searching, the *PNPLA3* rs738409 G genotype is one of the few confirmed genetic factors contributing to a patient's susceptibility to both ALD and NAFLD and to the progression of both diseases. Because this SNP may be useful in screening and managing high-risk patients and may constitute a therapeutic target, further studies are warranted.

PREDICTORS OF OUTCOMES

Predictors of hepatocarcinogenesis, hepatic decompensation, and mortality have been identified in patients with ALD and NAFLD (Table 3).

Hepatocarcinogenesis

Although a recent study of patients with compensated alcoholic cirrhosis failed to identify any risk factors significantly associated with hepatocarcinogenesis[90], a study of patients with decompensated alcoholic cirrhosis found that older age was significantly associated with hepatocarcinogenesis[91]. Moreover, the *PNPLA3* SNP was reported to be closely associated with the susceptibility to hepatocellular carcinoma (HCC) in patients with ALD[92,93].

Older age and alcohol intake were found to be independent risk factors for hepatocarcinogenesis in patients with NASH-related cirrhosis[94]. A multivariate analysis of a large number of Japanese patients with NAFLD found that older age, type 2 diabetes, an elevated serum AST concentration, and a low platelet count were significantly associated with hepatocarcinogenesis[95].

A recent study compared hepatocarcinogenesis in patients with alcoholic liver cirrhosis and NASH-related cirrhosis. A multivariate analysis revealed that older age, an elevated serum GGT concentration, and a higher Child-Pugh score were risk factors for the development of HCC in patients with NASH-related cirrhosis, whereas no factor was found to be significantly associated with hepatocarcinogenesis in patients with alcoholic cirrhosis[96].

Hepatic decompensation

Persistent alcohol intake has been reported to predict hepatic decompensation in patients with alcoholic cirrhosis[90]. To our knowledge, however, no studies to date

have assessed the risk factors for hepatic decompensation in patients with compensated NASH-related cirrhosis.

Mortality

A long-term cohort study analyzed the predictors of mortality in patients with ALD and simple hepatic steatosis and reported that a low serum albumin concentration and severe steatosis were significantly associated with increased mortality[55]. Moreover, persistent alcohol intake was found to be the only factor predictive of mortality in patients with compensated alcoholic cirrhosis[90]. A long-term follow-up study, in which most of the patients suffered from decompensated alcoholic cirrhosis, found that older age, alcohol abuse, and elevated alkaline phosphatase levels were risk factors for mortality[97]. In another long-term follow-up study involving patients with decompensated alcoholic cirrhosis, older age, persistent alcohol intake, a low serum albumin concentration, and a higher baseline model for end-stage liver disease (MELD) score were predictive of mortality[98]. Similarly, older age and poorer liver function were significantly associated with increased mortality in patients with decompensated alcoholic cirrhosis[91]. More recently, an analysis of patients with advanced, non-decompensated ALD revealed that smoking, a low serum albumin concentration, persistent alcohol intake, and older age were associated with increased mortality[99].

In patients with NAFLD and simple hepatic steatosis, only a low serum albumin concentration was found to be significantly associated with patient mortality[55]. A long-term cohort study involving patients with NAFLD found that an AST/ALT ratio > 1 and older age were associated with overall mortality, whereas higher serum bilirubin concentrations and stage 4 fibrosis were associated with liver-related mortality[100]. Older age and accompanying type 2 diabetes were significantly associated with increased mortality in patients with biopsy-proven NAFLD, whereas NASH, older age and type 2 diabetes were risk factors for liver-related mortality[101]. A recent, large population-based study revealed that metabolic syndrome was independently associated with overall mortality, liver-specific mortality, and cardiovascular mortality and that older age, smoking, and black race were risk factors for overall mortality[102].

A large cohort study found that type 2 diabetes and/or IR were independent predictors of overall mortality in patients with both ALD and NAFLD. Furthermore, type 2 diabetes, IR, obesity, and metabolic syndrome were independent predictors of liver-related mortality in both patient subsets[103].

COMORBIDITIES

ALD and NAFLD are frequently accompanied by extrahepatic complications. Therefore, we compared the comorbidities of patients with these two types of liver disease.

Metabolic syndrome and its related diseases

Excessive alcohol intake is highly associated with metabolic syndrome-related diseases, including hypertension, type 2 diabetes, and dyslipidemia[104-107], whereas NAFLD and metabolic syndrome are closely related[108]. Few studies to date have compared the associations of ALD and NAFLD with metabolic syndrome and/or related diseases. A recent study, however, found that an alcoholic fatty liver was more strongly associated with hypertension than a nonalcoholic fatty liver, whereas the latter was more strongly associated with dyslipidemia than the former[109]. Further studies are required to confirm these findings.

Cerebrovascular and cardiovascular diseases

Although little is known regarding the relationships between ALD and cerebrovascular and cardiovascular diseases, excessive alcohol intake has been reported to enhance the risks of these diseases, whereas light-to-moderate alcohol intake lowers these risks[110-112]. In comparison, a systematic review confirmed that NAFLD is an independent risk factor for cardiovascular disease[113], but it remains unclear whether NAFLD is a risk factor for cerebrovascular disease.

Extrahepatic malignancy

Although alcohol *per se* is not a carcinogen, excessive alcohol intake has been associated with HCC and other cancers, including oral cavity, pharyngeal, laryngeal, esophageal, colorectal, and female breast cancer[96,114]. A recent systematic review suggested a close relationship between NAFLD and colorectal cancer[113].

CHARACTERISTICS OF OUTCOMES

ALD and NAFLD are heterogeneous disorders that encompass a wide range of pathologies, from simple hepatic steatosis to liver cirrhosis and HCC. Furthermore, both diseases are frequently accompanied by extrahepatic complications. Patient survival can depend on various disease conditions. Although few studies to date have directly compared the outcomes of patients with ALD and NAFLD, we have delineated the characteristics of the reported outcomes (Table 4).

Hepatocarcinogenesis

The cumulative incidence rates of HCC were 6.8% at 10 years in ALD patients with compensated cirrhosis[90] and 7.1% at 5 years in patients with decompensated cirrhosis[91]. In contrast, a systematic review found that the cumulative incidence rate of HCC at up to 20 years in patients with NAFLD or NASH, of whom few or none had cirrhosis, was 0%-3%[115]. In patients with NASH and cirrhosis, the cumulative rates of HCC ranged from 2.4% over 7 years to 12.8% over 3 years[115]. A large Japanese study of patients with NAFLD found that the annual rate of new HCC cases was 0.043%[95]. More recently, the 5-year cumulative rates of HCC were found to be com-

Table 4 Outcome characteristics of patients with alcoholic liver disease and nonalcoholic fatty liver disease

Outcomes	ALD	NAFLD	Ref.
Hepatocarcinogenesis			
Incidence rate			
Simple hepatic steatosis/steatohepatitis		0%-0.2% per year	[115]
Steatohepatitis/cirrhosis		0.3%-4.3% per year	[115]
Compensated cirrhosis	0.7% per year		[90]
Decompensated cirrhosis	1.4% per year		[91]
Compensated/decompensated cirrhosis	2.5% per year	2.1% per year	[96]
Unknown stage		0.043% per year	[95]
Prevalence rate of non-cirrhotic liver as underlying liver disease	5.3%-12.0%	25.0%-58.3%	[116-118]
Comparison of survival	Similar to non-ALD, NBNC HCC	Better than ALD- or HCV-related HCC	[119,120]
Hepatic decompensation			
Incidence rate			
Compensated cirrhosis	4.4% per year	4.5% per year	[90,121]
Mortality (overall)			
Incidence rate			
Simple hepatic steatosis	3.3% per year		[52]
Steatohepatitis	5.0% per year		[52]
Steatohepatitis/cirrhosis		1.8% per year	[100]
Compensated cirrhosis	3.2% per year		[90]
Decompensated cirrhosis	5.7%-6.0% per year		[91,97]
Compensated/decompensated cirrhosis		5.0% per year	[124]
Compared with liver diseases due to other causes		Similar to HCV-related compensated liver disease	[100]
	Similar to HCV-related compensated cirrhosis	Better than HCV-related compensated cirrhosis	[90,122]
	Similar to HCV-related decompensated cirrhosis	Similar to HCV-related decompensated cirrhosis	[91,122]
		Similar to HCV-related cirrhosis	[124]
Improved survival	Abstinence		[123]
Causes of death			
Simple hepatic steatosis			[55]
Liver-related causes	17%	2%	
Arteriosclerosis	20%	38%	
Extrahepatic malignancy	14%	17%	
Infection	3%	8%	
Cirrhosis			[90,97,98,122,124]
HCC	10%-13%	6.9%-47.4%	
Liver failure	25%-60%	17.2%-31.6%	
Cardiovascular disease	1%	27.6%	
Cerebrovascular disease	1%-4%		
Infection	8.9%-25%	41.4%	
Extrahepatic malignancy	8%-25%		

ALD: Alcoholic liver disease; NAFLD: Nonalcoholic fatty liver disease; HCC: Hepatocellular carcinoma; NBNC: Non-B, non-C; HCV: Hepatitis C virus.

parable in patients with alcoholic (12.5%) and NASH-related (10.5%) cirrhosis[96].

Collectively, the incidence of HCC seems to be somewhat higher in patients with ALD than in patients with NAFLD. Most (88.0%-94.7%) ALD-related HCCs arise from cirrhosis, whereas 41.7%-75.0% of NAFLD-related HCCs arise from a non-cirrhotic liver[116-118]. Moreover, there was no difference in age between the patients with ALD-related HCC and those with NAFLD-related HCC, although the percentage of females was lower in the former than in the latter[116,119].

To our knowledge, no studies to date have compared the outcomes of patients with ALD- and NAFLD-related HCC. A study of patients who had non-hepatitis B/non-hepatitis C HCC found that the survival rates were similar between the patients with ALD-related HCC and those with non-ALD-related HCC, whereas the tumor recurrence rate was higher in the ALD group[120]. A comparison of the outcomes of curative treatment for HCC in patients with NASH and those with ALD or hepatitis C-related liver disease revealed that the cause of liver disease did not influence the recurrence-free survival according to a multivariate analysis, whereas NASH was significantly associated with an improved overall survival[119].

Hepatic decompensation

A study of the natural history of alcoholic cirrhosis found that the cumulative 10 year hepatic decompensation rate was 37.4%[90]. During the follow-up, only approximately one-fourth of these patients abstained from

alcohol. In contrast, 45% of patients with compensated NASH-related cirrhosis developed hepatic decompensation during a follow-up of 10 years[121]. Ascites, a manifestation of hepatic decompensation, is frequently observed in patients with alcoholic cirrhosis[90,98,122], but the incidence of ascites is relatively low in patients with NASH-related cirrhosis[121].

Mortality and causes of death

The cumulative 5-year survival rates of patients with ALD were reported to be 83.3% in patients with simple hepatic steatosis and 74.9% in those with alcoholic steatohepatitis[52]. Furthermore, the cumulative 5-year survival rates in patients with compensated and decompensated alcoholic cirrhosis were reported to be 83.9%[90] and 71.3%[91], respectively. Abstinence from alcohol has the potential to increase the survival of patients with alcoholic cirrhosis[123]. In a study of the survival of patients with decompensated alcoholic and hepatitis C-related cirrhosis, a multivariate analysis revealed that the cause of liver disease did not affect survival[91].

A comparison of patients with NASH-related cirrhosis (mean Child-Pugh score 6.1) and hepatitis C-related cirrhosis (mean Child-Pugh score 6.1) revealed that the cumulative 5-year survival rates were 75.2% and 73.8%, respectively[124]. A similar study examining the natural history of advanced fibrosis or compensated cirrhosis due to either NASH or hepatitis C found that the 10-year cumulative survival rates were 81.6% and 82.0%, respectively[100].

A recent study of patients with NASH-related or alcoholic cirrhosis who underwent liver transplantation found no significant differences in the post-transplant survival and cardiovascular mortality rates. However, cardiovascular causes of post-transplant death were more frequent in the NASH group, while malignancies were more frequent in the alcoholic group[125]. In addition, studies have reported that the overall survival after liver transplantation was excellent in patients with HCC and ALD or NAFLD[126,127].

The causes of death have been found to differ in patients with ALD and NAFLD. A long-term follow-up of patients with simple hepatic steatosis revealed that many of the patients with ALD and NAFLD died of extrahepatic, rather than hepatic, causes. For example, the main causes of death in ALD patients were arteriosclerosis (20%), liver cirrhosis (17%), unknown causes (16%), and extrahepatic cancers (14%), whereas the main causes of death in NAFLD patients were arteriosclerosis (38%), unknown causes (19%), extrahepatic cancers (17%), and infections (8%)[55]. Similarly, studies of patients with alcoholic cirrhosis indicated that a significant percentage of individuals died of extrahepatic causes, with the leading causes being liver failure (25.0%-36.0%), bacterial infection (11.5%-25.0%), extrahepatic cancers (8.0%-25.0%), and HCC (12.5%-13.0%)[90,98]. A population-based study found that ALD contributed to liver-related but not cardiovascular mortality[128]. Moreover, recent studies of patients with histologically proven NAFLD, of whom 41.6%-59.2% had NASH, found that the leading causes of death were cardiovascular disease (27.8%-28.2%), liver-related causes (15.4%-26.1%), and extrahepatic malignancy (15.7%-17.9%)[101,129]. Similar patterns were observed in other studies of patients with NAFLD, with the leading causes of death being extrahepatic malignancy (28.0%-33.3%), liver-related complications (12.8%-19.0%), and cardiovascular disease (19.0%-25.0%)[130-133]. In one study of patients with NASH-related cirrhosis, the major causes of death were infection (41.4%), cardiovascular disease (27.6%), and liver-related complications (24.1%)[121], whereas the causes were HCC (47.4%) and liver failure (31.6%) in a second study[124].

In summary, the mortality rates of patients with ALD and NAFLD were found to be similar, although the causes of death differed somewhat. When compared with patients with hepatitis C, larger percentages of patients with ALD and NAFLD died of extrahepatic causes; many ALD patients died of infection and extrahepatic cancers, and many NAFLD patients died of cardiovascular disease.

CONCLUSION

In this review, we attempted to delineate the characteristics and outcomes of patients with ALD and NAFLD, particularly from a clinical aspect. Both liver diseases are generally related to unhealthy lifestyle habits, including excessive alcohol and food intake, and both are likely to be serious health problems in the future. In contrast to chronic viral liver diseases, ALD and NAFLD are frequently accompanied by extrahepatic diseases that can influence patient survival. A comprehensive understanding of these diseases is essential for their management.

REFERENCES

1 **Rehm J**, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet* 2009; **373**: 2223-2233 [PMID: 19560604 DOI: 10.1016/S0140-6736(09)60746-7]

2 **Schwartz JM**, Reinus JF. Prevalence and natural history of alcoholic liver disease. *Clin Liver Dis* 2012; **16**: 659-666 [PMID: 23101975 DOI: 10.1016/j.cld.2012.08.001]

3 **Mohapatra S**, Patra J, Popova S, Duhig A, Rehm J. Social cost of heavy drinking and alcohol dependence in high-income countries. *Int J Public Health* 2010; **55**: 149-157 [PMID: 20024666 DOI: 10.1007/s00038-009-0108-9]

4 **Finucane MM**, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, Singh GM, Gutierrez HR, Lu Y, Bahalim AN, Farzadfar F, Riley LM, Ezzati M. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *Lancet* 2011; **377**: 557-567 [PMID: 21295846 DOI: 10.1016/S0140-6736(10)62037-5]

5 **Marchesini G**, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003; **37**: 917-923 [PMID:

12668987 DOI: 10.1053/jhep.2003.50161]
6 **Boudreau DM**, Malone DC, Raebel MA, Fishman PA, Nichols GA, Feldstein AC, Boscoe AN, Ben-Joseph RH, Magid DJ, Okamoto LJ. Health care utilization and costs by metabolic syndrome risk factors. *Metab Syndr Relat Disord* 2009; **7**: 305-314 [PMID: 19558267 DOI: 10.1089/met.2008.0070]
7 **Tannapfel A**, Denk H, Dienes HP, Langner C, Schirmacher P, Trauner M, Flott-Rahmel B. Histopathological diagnosis of non-alcoholic and alcoholic fatty liver disease. *Virchows Arch* 2011; **458**: 511-523 [PMID: 21442288 DOI: 10.1007/s00428-011-1066-1]
8 **Rehm J**, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. *J Hepatol* 2013; **59**: 160-168 [PMID: 23511777 DOI: 10.1016/j.jhep.2013.03.007]
9 **Hamaguchi M**, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, Omatsu T, Nakajima T, Sarui H, Shimazaki M, Kato T, Okuda J, Ida K. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med* 2005; **143**: 722-728 [PMID: 16287793]
10 **Adams LA**, Lindor KD. Nonalcoholic fatty liver disease. *Ann Epidemiol* 2007; **17**: 863-869 [PMID: 17728149 DOI: 10.1016/j.annepidem.2007.05.013]
11 **Williams CD**, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, Landt CL, Harrison SA. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology* 2011; **140**: 124-131 [PMID: 20858492 DOI: 10.1053/j.gastro.2010.09.038]
12 **Eguchi Y**, Hyogo H, Ono M, Mizuta T, Ono N, Fujimoto K, Chayama K, Saibara T. Prevalence and associated metabolic factors of nonalcoholic fatty liver disease in the general population from 2009 to 2010 in Japan: a multicenter large retrospective study. *J Gastroenterol* 2012; **47**: 586-595 [PMID: 22328022 DOI: 10.1007/s00535-012-0533-z]
13 **Kojima S**, Watanabe N, Numata M, Ogawa T, Matsuzaki S. Increase in the prevalence of fatty liver in Japan over the past 12 years: analysis of clinical background. *J Gastroenterol* 2003; **38**: 954-961 [PMID: 14614602 DOI: 10.1007/s00535-003-1178-8]
14 **Fan JG**. Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. *J Gastroenterol Hepatol* 2013; **28** Suppl 1: 11-17 [PMID: 23855290 DOI: 10.1111/jgh.12036]
15 **Adams WL**, Yuan Z, Barboriak JJ, Rimm AA. Alcohol-related hospitalizations of elderly people. Prevalence and geographic variation in the United States. *JAMA* 1993; **270**: 1222-1225 [PMID: 8355385]
16 **Fan JG**, Zhu J, Li XJ, Chen L, Li L, Dai F, Li F, Chen SY. Prevalence of and risk factors for fatty liver in a general population of Shanghai, China. *J Hepatol* 2005; **43**: 508-514 [PMID: 16006003 DOI: 10.1016/j.jhep.2005.02.042]
17 **Schwimmer JB**, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. *Pediatrics* 2006; **118**: 1388-1393 [PMID: 17015527 DOI: 10.1542/peds.2006-1212]
18 **Bellentani S**, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, Saveria Crocè L, Sasso F, Pozzato G, Cristianini G, Brandi G. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. *Gut* 1997; **41**: 845-850 [PMID: 9462221]
19 **Yang AL**, Vadhavkar S, Singh G, Omary MB. Epidemiology of alcohol-related liver and pancreatic disease in the United States. *Arch Intern Med* 2008; **168**: 649-656 [PMID: 18362258 DOI: 10.1001/archinte.168.6.649]
20 **Shen L**, Fan JG, Shao Y, Zeng MD, Wang JR, Luo GH, Li JQ, Chen SY. Prevalence of nonalcoholic fatty liver among administrative officers in Shanghai: an epidemiological survey. *World J Gastroenterol* 2003; **9**: 1106-1110 [PMID: 12717867]
21 **Douds AC**, Cox MA, Iqbal TH, Cooper BT. Ethnic differences in cirrhosis of the liver in a British city: alcoholic cirrhosis in South Asian men. *Alcohol Alcohol* 2003; **38**: 148-150 [PMID: 12634262]
22 **Lazo M**, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, Koteish A, Brancati FL, Clark JM. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988-1994. *Am J Epidemiol* 2013; **178**: 38-45 [PMID: 23703888 DOI: 10.1093/aje/kws448]
23 **McCullough AJ**. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. *Clin Liver Dis* 2004; **8**: 521-33, viii [PMID: 15331061 DOI: 10.1016/j.cld.2004.04.004]
24 **Hock B**, Schwarz M, Domke I, Grunert VP, Wuertemberger M, Schiemann U, Horster S, Limmer C, Stecker G, Soyka M. Validity of carbohydrate-deficient transferrin (%CDT), gamma-glutamyltransferase (gamma-GT) and mean corpuscular erythrocyte volume (MCV) as biomarkers for chronic alcohol abuse: a study in patients with alcohol dependence and liver disorders of non-alcoholic and alcoholic origin. *Addiction* 2005; **100**: 1477-1486 [PMID: 16185209 DOI: 10.1111/j.1360-0443.2005.01216.x]
25 **Dunn W**, Angulo P, Sanderson S, Jamil LH, Stadheim L, Rosen C, Malinchoc M, Kamath PS, Shah VH. Utility of a new model to diagnose an alcohol basis for steatohepatitis. *Gastroenterology* 2006; **131**: 1057-1063 [PMID: 17030176 DOI: 10.1053/j.gastro.2006.08.020]
26 **Imbert-Bismut F**, Naveau S, Morra R, Munteanu M, Ratziu V, Abella A, Messous D, Thabut D, Benhamou Y, Poynard T. The diagnostic value of combining carbohydrate-deficient transferrin, fibrosis, and steatosis biomarkers for the prediction of excessive alcohol consumption. *Eur J Gastroenterol Hepatol* 2009; **21**: 18-27 [PMID: 19011575 DOI: 10.1097/MEG.0b013e32830a4f4c]
27 **Cerović I**, Mladenović D, Ješić R, Naumović T, Branković M, Vučević D, Aleksić V, Radosavljević T. Alcoholic liver disease/nonalcoholic fatty liver disease index: distinguishing alcoholic from nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol* 2013; **25**: 899-904 [PMID: 23426271 DOI: 10.1097/MEG.0b013e32835f0786]
28 **Baršić N**, Lerotić I, Smirčić-Duvnjak L, Tomašić V, Duvnjak M. Overview and developments in noninvasive diagnosis of nonalcoholic fatty liver disease. *World J Gastroenterol* 2012; **18**: 3945-3954 [PMID: 22912545 DOI: 10.3748/wjg.v18.i30.3945]
29 **Wai CT**, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; **38**: 518-526 [PMID: 12883497 DOI: 10.1053/jhep.2003.50346]
30 **Sterling RK**, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, S Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL, Messinger D, Nelson M. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology* 2006; **43**: 1317-1325 [PMID: 16729309 DOI: 10.1002/hep.21178]
31 **Imbert-Bismut F**, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001; **357**: 1069-1075 [PMID: 11297957 DOI: 10.1016/S0140-6736(00)04258-6]
32 **Naveau S**, Raynard B, Ratziu V, Abella A, Imbert-Bismut F, Messous D, Beuzen F, Capron F, Thabut D, Munteanu M, Chaput JC, Poynard T. Biomarkers for the prediction of liver fibrosis in patients with chronic alcoholic liver disease. *Clin Gastroenterol Hepatol* 2005; **3**: 167-174 [PMID: 15704051]
33 **Naveau S**, Gaudé G, Asnacios A, Agostini H, Abella A, Barri-Ova N, Dauvois B, Prévot S, Ngo Y, Munteanu M, Balian A, Njiké-Nakseu M, Perlemuter G, Poynard T. Diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with alcoholic liver disease. *Hepatology* 2009; **49**: 97-105 [PMID: 19053048 DOI: 10.1002/hep.22576]

34 **Shah AG**, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2009; **7**: 1104-1112 [PMID: 19523535 DOI: 10.1016/j.cgh.2009.05.033]

35 **Sumida Y**, Yoneda M, Hyogo H, Itoh Y, Ono M, Fujii H, Eguchi Y, Suzuki Y, Aoki N, Kanemasa K, Fujita K, Chayama K, Saibara T, Kawada N, Fujimoto K, Kohgo Y, Yoshikawa T, Okanoue T. Validation of the FIB4 index in a Japanese nonalcoholic fatty liver disease population. *BMC Gastroenterol* 2012; **12**: 2 [PMID: 22221544 DOI: 10.1186/1471-230X-12-2]

36 **Ratziu V**, Massard J, Charlotte F, Messous D, Imbert-Bismut F, Bonyhay L, Tahiri M, Munteanu M, Thabut D, Cadranel JF, Le Bail B, de Ledinghen V, Poynard T. Diagnostic value of biochemical markers (FibroTest-FibroSURE) for the prediction of liver fibrosis in patients with non-alcoholic fatty liver disease. *BMC Gastroenterol* 2006; **6**: 6 [PMID: 16503961 DOI: 10.1186/1471-230X-6-6]

37 **Nahon P**, Kettaneh A, Tengher-Barna I, Ziol M, de Lédinghen V, Douvin C, Marcellin P, Ganne-Carrié N, Trinchet JC, Beaugrand M. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. *J Hepatol* 2008; **49**: 1062-1068 [PMID: 18930329 DOI: 10.1016/j.jhep.2008.08.011]

38 **Wong VW**, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, Choi PC, Kowo M, Chan AW, Merrouche W, Sung JJ, de Lédinghen V. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology* 2010; **51**: 454-462 [PMID: 20101745 DOI: 10.1002/hep.23312]

39 **Sasso M**, Beaugrand M, de Ledinghen V, Douvin C, Marcellin P, Poupon R, Sandrin L, Miette V. Controlled attenuation parameter (CAP): a novel VCTE™ guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. *Ultrasound Med Biol* 2010; **36**: 1825-1835 [PMID: 20870345 DOI: 10.1016/j.ultrasmedbio.2010.07.005]

40 **Myers RP**, Pollett A, Kirsch R, Pomier-Layrargues G, Beaton M, Levstik M, Duarte-Rojo A, Wong D, Crotty P, Elkashab M. Controlled Attenuation Parameter (CAP): a noninvasive method for the detection of hepatic steatosis based on transient elastography. *Liver Int* 2012; **32**: 902-910 [PMID: 22435761 DOI: 10.1111/j.1478-3231.2012.02781.x]

41 **de Lédinghen V**, Vergniol J, Foucher J, Merrouche W, le Bail B. Non-invasive diagnosis of liver steatosis using controlled attenuation parameter (CAP) and transient elastography. *Liver Int* 2012; **32**: 911-918 [PMID: 22672642 DOI: 10.1111/j.1478-3231.2012.02820.x]

42 **de Lédinghen V**, Vergniol J, Capdepont M, Chermak F, Hiriart JB, Cassinotto C, Merrouche W, Foucher J, Brigitte le B. Controlled attenuation parameter (CAP) for the diagnosis of steatosis: a prospective study of 5323 examinations. *J Hepatol* 2014; **60**: 1026-1031 [PMID: 24378529 DOI: 10.1016/j.jhep.2013.12.018]

43 **Lucey MR**, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med* 2009; **360**: 2758-2769 [PMID: 19553649 DOI: 10.1056/NEJMra0805786]

44 **Lafferty H**, Stanley AJ, Forrest EH. The management of alcoholic hepatitis: a prospective comparison of scoring systems. *Aliment Pharmacol Ther* 2013; **38**: 603-610 [PMID: 23879668 DOI: 10.1111/apt.12414]

45 **Kadian M**, Kakkar R, Dhar M, Kaushik RM. Model for end-stage liver disease score versus Maddrey discriminant function score in assessing short-term outcome in alcoholic hepatitis. *J Gastroenterol Hepatol* 2014; **29**: 581-588 [PMID: 24117536 DOI: 10.1111/jgh.12400]

46 **Brunt EM**, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* 1999; **94**: 2467-2474 [PMID: 10484010 DOI: 10.1111/j.1572-0241.1999.01377.x]

47 **Kleiner DE**, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; **41**: 1313-1321 [PMID: 15915461 DOI: 10.1002/hep.20701]

48 **Hjelkrem M**, Stauch C, Shaw J, Harrison SA. Validation of the non-alcoholic fatty liver disease activity score. *Aliment Pharmacol Ther* 2011; **34**: 214-218 [PMID: 21585409 DOI: 10.1111/j.1365-2036.2011.04695.x]

49 **Vuppalanchi R**, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. *Hepatology* 2009; **49**: 306-317 [PMID: 19065650 DOI: 10.1002/hep.22603]

50 **Sullivan S**. Implications of diet on nonalcoholic fatty liver disease. *Curr Opin Gastroenterol* 2010; **26**: 160-164 [PMID: 20010099 DOI: 10.1097/MOG.0b013e3283358a58]

51 **Mathurin P**, Beuzin F, Louvet A, Carrié-Ganne N, Balian A, Trinchet JC, Dalsoglio D, Prevot S, Naveau S. Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features. *Aliment Pharmacol Ther* 2007; **25**: 1047-1054 [PMID: 17439505 DOI: 10.1111/j.1365-2036.2007.03302.x]

52 **Deleuran T**, Grønbaek H, Vilstrup H, Jepsen P. Cirrhosis and mortality risks of biopsy-verified alcoholic pure steatosis and steatohepatitis: a nationwide registry-based study. *Aliment Pharmacol Ther* 2012; **35**: 1336-1342 [PMID: 22490057 DOI: 10.1111/j.1365-2036.2012.05091.x]

53 **Adams LA**, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005; **42**: 132-138 [PMID: 15629518 DOI: 10.1016/j.jhep.2004.09.012]

54 **Ekstedt M**, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, Kechagias S. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006; **44**: 865-873 [PMID: 17006923 DOI: 10.1002/hep.21327]

55 **Dam-Larsen S**, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. *Scand J Gastroenterol* 2009; **44**: 1236-1243 [PMID: 19670076 DOI: 10.1080/00365520903171284]

56 **Dunn W**, Zeng Z, O'Neil M, Zhao J, Whitener M, Yu-Jui Wan Y, Mitchell EK, Handler M, Weinman SA. The interaction of rs738409, obesity, and alcohol: a population-based autopsy study. *Am J Gastroenterol* 2012; **107**: 1668-1674 [PMID: 23032985 DOI: 10.1038/ajg.2012.285]

57 **Becker U**, Deis A, Sørensen TI, Grønbaek M, Borch-Johnsen K, Müller CF, Schnohr P, Jensen G. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology* 1996; **23**: 1025-1029 [PMID: 8621128 DOI: 10.1002/hep.510230513]

58 **Naveau S**, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. *Hepatology* 1997; **25**: 108-111 [PMID: 8985274 DOI: 10.1002/hep.510250120]

59 **Kerr WC**, Fillmore KM, Marvy P. Beverage-specific alcohol consumption and cirrhosis mortality in a group of English-speaking beer-drinking countries. *Addiction* 2000; **95**: 339-346 [PMID: 10795350]

60 **Hatton J**, Burton A, Nash H, Munn E, Burgoyne L, Sheron N. Drinking patterns, dependency and life-time drinking history in alcohol-related liver disease. *Addiction* 2009; **104**: 587-592 [PMID: 19215600 DOI: 10.1111/j.1360-0443.2008.02493.x]

61 **Zelber-Sagi S**, Nitzan-Kaluski D, Goldsmith R, Webb M, Blendis L, Halpern Z, Oren R. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): a population based study. *J Hepatol* 2007; **47**: 711-717 [PMID:

17850914 DOI: 10.1016/j.jhep.2007.06.020]
62 **Abdelmalek MF**, Suzuki A, Guy C, Unalp-Arida A, Colvin R, Johnson RJ, Diehl AM. Increased fructose consumption is associated with fibrosis severity in patients with nonalcoholic fatty liver disease. *Hepatology* 2010; **51**: 1961-1971 [PMID: 20301112 DOI: 10.1002/hep.23535]
63 **Ouyang X**, Cirillo P, Sautin Y, McCall S, Bruchette JL, Diehl AM, Johnson RJ, Abdelmalek MF. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. *J Hepatol* 2008; **48**: 993-999 [PMID: 18395287 DOI: 10.1016/j.jhep.2008.02.011]
64 **Spadaro L**, Magliocco O, Spampinato D, Piro S, Oliveri C, Alagona C, Papa G, Rabuazzo AM, Purrello F. Effects of n-3 polyunsaturated fatty acids in subjects with nonalcoholic fatty liver disease. *Dig Liver Dis* 2008; **40**: 194-199 [PMID: 18054848 DOI: 10.1016/j.dld.2007.10.003]
65 **Seitz HK**, Stickel F. Alcoholic liver disease in the elderly. *Clin Geriatr Med* 2007; **23**: 905-21, viii [PMID: 17923345 DOI: 10.1016/j.cger.2007.06.010]
66 **Meier P**, Seitz HK. Age, alcohol metabolism and liver disease. *Curr Opin Clin Nutr Metab Care* 2008; **11**: 21-26 [PMID: 18090653 DOI: 10.1097/MCO.0b013e3282f30564]
67 **Raynard B**, Balian A, Fallik D, Capron F, Bedossa P, Chaput JC, Naveau S. Risk factors of fibrosis in alcohol-induced liver disease. *Hepatology* 2002; **35**: 635-638 [PMID: 11870378 DOI: 10.1053/jhep.2002.31782]
68 **Argo CK**, Northup PG, Al-Osaimi AM, Caldwell SH. Systematic review of risk factors for fibrosis progression in non-alcoholic steatohepatitis. *J Hepatol* 2009; **51**: 371-379 [PMID: 19501928 DOI: 10.1016/j.jhep.2009.03.019]
69 **Cornier MA**, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, Van Pelt RE, Wang H, Eckel RH. The metabolic syndrome. *Endocr Rev* 2008; **29**: 777-822 [PMID: 18971485 DOI: 10.1210/er.2008-0024]
70 **Longato L**, Ripp K, Setshedi M, Dostalek M, Akhlaghi F, Branda M, Wands JR, de la Monte SM. Insulin resistance, ceramide accumulation, and endoplasmic reticulum stress in human chronic alcohol-related liver disease. *Oxid Med Cell Longev* 2012; **2012**: 479348 [PMID: 22577490 DOI: 10.1155/2012/479348]
71 **Kotronen A**, Yki-Järvinen H, Männistö S, Saarikoski L, Korpi-Hyövälti E, Oksa H, Saltevo J, Saaristo T, Sundvall J, Tuomilehto J, Peltonen M. Non-alcoholic and alcoholic fatty liver disease - two diseases of affluence associated with the metabolic syndrome and type 2 diabetes: the FIN-D2D survey. *BMC Public Health* 2010; **10**: 237 [PMID: 20459722 DOI: 10.1186/1471-2458-10-237]
72 **Dixon JB**, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology* 2001; **121**: 91-100 [PMID: 11438497]
73 **Stewart SH**. Racial and ethnic differences in alcohol-associated aspartate aminotransferase and gamma-glutamyltransferase elevation. *Arch Intern Med* 2002; **162**: 2236-2239 [PMID: 12390068]
74 **Stranges S**, Freudenheim JL, Muti P, Farinaro E, Russell M, Nochajski TH, Trevisan M. Greater hepatic vulnerability after alcohol intake in African Americans compared with Caucasians: a population-based study. *J Natl Med Assoc* 2004; **96**: 1185-1192 [PMID: 15481746]
75 **Bambha K**, Belt P, Abraham M, Wilson LA, Pabst M, Ferrell L, Unalp-Arida A, Bass N. Ethnicity and nonalcoholic fatty liver disease. *Hepatology* 2012; **55**: 769-780 [PMID: 21987488 DOI: 10.1002/hep.24726]
76 **Stickel F**, Hampe J. Genetic determinants of alcoholic liver disease. *Gut* 2012; **61**: 150-159 [PMID: 22110053 DOI: 10.1136/gutjnl-2011-301239]
77 **Daly AK**, Ballestri S, Carulli L, Loria P, Day CP. Genetic determinants of susceptibility and severity in nonalcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol* 2011; **5**: 253-263 [PMID: 21476920 DOI: 10.1586/egh.11.18]
78 **Wilson PA**, Gardner SD, Lambie NM, Commans SA, Crowther DJ. Characterization of the human patatin-like phospholipase family. *J Lipid Res* 2006; **47**: 1940-1949 [PMID: 16799181 DOI: 10.1194/jlr.M600185-JLR200]
79 **Sookoian S**, Pirola CJ. The genetic epidemiology of non-alcoholic fatty liver disease: toward a personalized medicine. *Clin Liver Dis* 2012; **16**: 467-485 [PMID: 22824476 DOI: 10.1016/j.cld.2012.05.011]
80 **Romeo S**, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008; **40**: 1461-1465 [PMID: 18820647 DOI: 10.1038/ng.257]
81 **Sookoian S**, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology* 2011; **53**: 1883-1894 [PMID: 21381068 DOI: 10.1002/hep.24283]
82 **Tian C**, Stokowski RP, Kershenobich D, Ballinger DG, Hinds DA. Variant in PNPLA3 is associated with alcoholic liver disease. *Nat Genet* 2010; **42**: 21-23 [PMID: 19946271 DOI: 10.1038/ng.488]
83 **Stickel F**, Buch S, Lau K, Meyer zu Schwabedissen H, Berg T, Ridinger M, Rietschel M, Schafmayer C, Braun F, Hinrichsen H, Günther R, Arlt A, Seeger M, Müller S, Seitz HK, Soyka M, Lerch M, Lammert F, Sarrazin C, Kubitz R, Häussinger D, Hellerbrand C, Bröring D, Schreiber S, Kiefer F, Spanagel R, Mann K, Datz C, Krawczak M, Wodarz N, Völzke H, Hampe J. Genetic variation in the PNPLA3 gene is associated with alcoholic liver injury in caucasians. *Hepatology* 2011; **53**: 86-95 [PMID: 21254164 DOI: 10.1002/hep.24017]
84 **Trépo E**, Gustot T, Degré D, Lemmers A, Verset L, Demetter P, Ouziel R, Quertinmont E, Vercruysse V, Amininejad L, Deltenre P, Le Moine O, Devière J, Franchimont D, Moreno C. Common polymorphism in the PNPLA3/adiponutrin gene confers higher risk of cirrhosis and liver damage in alcoholic liver disease. *J Hepatol* 2011; **55**: 906-912 [PMID: 21334404 DOI: 10.1016/j.jhep.2011.01.028]
85 **Kawaguchi T**, Sumida Y, Umemura A, Matsuo K, Takahashi M, Takamura T, Yasui K, Saibara T, Hashimoto E, Kawanaka M, Watanabe S, Kawata S, Imai Y, Kokubo M, Shima T, Park H, Tanaka H, Tajima K, Yamada R, Matsuda F. Genetic polymorphisms of the human PNPLA3 gene are strongly associated with severity of non-alcoholic fatty liver disease in Japanese. *PLoS One* 2012; **7**: e38322 [PMID: 22719876 DOI: 10.1371/journal.pone.0038322]
86 **Kitamoto T**, Kitamoto A, Yoneda M, Hyogo H, Ochi H, Nakamura T, Teranishi H, Mizusawa S, Ueno T, Chayama K, Nakajima A, Nakao K, Sekine A, Hotta K. Genome-wide scan revealed that polymorphisms in the PNPLA3, SAMM50, and PARVB genes are associated with development and progression of nonalcoholic fatty liver disease in Japan. *Hum Genet* 2013; **132**: 783-792 [PMID: 23535911 DOI: 10.1007/s00439-013-1294-3]
87 **Chalasani N**, Guo X, Loomba R, Goodarzi MO, Haritunians T, Kwon S, Cui J, Taylor KD, Wilson L, Cummings OW, Chen YD, Rotter JI. Genome-wide association study identifies variants associated with histologic features of nonalcoholic Fatty liver disease. *Gastroenterology* 2010; **139**: 1567-176, 1576.e1-6 [PMID: 20708005 DOI: 10.1053/j.gastro.2010.07.057]
88 **Speliotes EK**, Yerges-Armstrong LM, Wu J, Hernaez R, Kim LJ, Palmer CD, Gudnason V, Eiriksdottir G, Garcia ME, Launer LJ, Nalls MA, Clark JM, Mitchell BD, Shuldiner AR, Butler JL, Tomas M, Hoffmann U, Hwang SJ, Massaro JM, O'Donnell CJ, Sahani DV, Salomaa V, Schadt EE, Schwartz SM, Siscovick DS, Voight BF, Carr JJ, Feitosa MF, Harris TB, Fox CS, Smith AV, Kao WH, Hirschhorn JN, Borecki IB. Genome-wide association analysis identifies variants associated with nonalcoholic fatty liver disease that have distinct

effects on metabolic traits. *PLoS Genet* 2011; **7**: e1001324 [PMID: 21423719 DOI: 10.1371/journal.pgen.1001324]
89 **Marcos M**, Gómez-Munuera M, Pastor I, González-Sarmiento R, Laso FJ. Tumor necrosis factor polymorphisms and alcoholic liver disease: a HuGE review and meta-analysis. *Am J Epidemiol* 2009; **170**: 948-956 [PMID: 19755636 DOI: 10.1093/aje/kwp236]
90 **Toshikuni N**, Izumi A, Nishino K, Inada N, Sakanoue R, Yamato R, Suehiro M, Kawanaka M, Yamada G. Comparison of outcomes between patients with alcoholic cirrhosis and those with hepatitis C virus-related cirrhosis. *J Gastroenterol Hepatol* 2009; **24**: 1276-1283 [PMID: 19486451 DOI: 10.1111/j.1440-1746.2009.05851.x]
91 **Solà R**, Alvarez MA, Ballesté B, Montoliu S, Rivera M, Miquel M, Cirera I, Morillas RM, Coll S, Planas R. Probability of liver cancer and survival in HCV-related or alcoholic-decompensated cirrhosis. A study of 377 patients. *Liver Int* 2006; **26**: 62-72 [PMID: 16420511 DOI: 10.1111/j.1478-3231.2005.01181.x]
92 **Nischalke HD**, Berger C, Luda C, Berg T, Müller T, Grünhage F, Lammert F, Coenen M, Krämer B, Körner C, Vidovic N, Oldenburg J, Nattermann J, Sauerbruch T, Spengler U. The PNPLA3 rs738409 148M/M genotype is a risk factor for liver cancer in alcoholic cirrhosis but shows no or weak association in hepatitis C cirrhosis. *PLoS One* 2011; **6**: e27087 [PMID: 22087248 DOI: 10.1371/journal.pone.0027087]
93 **Guyot E**, Sutton A, Rufat P, Laguillier C, Mansouri A, Moreau R, Ganne-Carrié N, Beaugrand M, Charnaux N, Trinchet JC, Nahon P. PNPLA3 rs738409, hepatocellular carcinoma occurrence and risk model prediction in patients with cirrhosis. *J Hepatol* 2013; **58**: 312-318 [PMID: 23069476 DOI: 10.1016/j.jhep.2012.09.036]
94 **Ascha MS**, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 1972-1978 [PMID: 20209604 DOI: 10.1002/hep.23527]
95 **Kawamura Y**, Arase Y, Ikeda K, Seko Y, Imai N, Hosaka T, Kobayashi M, Saitoh S, Sezaki H, Akuta N, Suzuki F, Suzuki Y, Ohmoto Y, Amakawa K, Tsuji H, Kumada H. Large-scale long-term follow-up study of Japanese patients with non-alcoholic Fatty liver disease for the onset of hepatocellular carcinoma. *Am J Gastroenterol* 2012; **107**: 253-261 [PMID: 22008893 DOI: 10.1038/ajg.2011.327]
96 **Kodama K**, Tokushige K, Hashimoto E, Taniai M, Shiratori K. Hepatic and extrahepatic malignancies in cirrhosis caused by nonalcoholic steatohepatitis and alcoholic liver disease. *Alcohol Clin Exp Res* 2013; **37** Suppl 1: E247-E252 [PMID: 23320802 DOI: 10.1111/j.1530-0277.2012.01900.x]
97 **Bell H**, Jahnsen J, Kittang E, Raknerud N, Sandvik L. Long-term prognosis of patients with alcoholic liver cirrhosis: a 15-year follow-up study of 100 Norwegian patients admitted to one unit. *Scand J Gastroenterol* 2004; **39**: 858-863 [PMID: 15513384 DOI: 10.1080/00365520410006350]
98 **Alvarez MA**, Cirera I, Solà R, Bargalló A, Morillas RM, Planas R. Long-term clinical course of decompensated alcoholic cirrhosis: a prospective study of 165 patients. *J Clin Gastroenterol* 2011; **45**: 906-911 [PMID: 21814145 DOI: 10.1097/MCG.0b013e3182284e13]
99 **Masson S**, Emmerson I, Henderson E, Fletcher EH, Burt AD, Day CP, Stewart SF. Clinical but not histological factors predict long-term prognosis in patients with histologically advanced non-decompensated alcoholic liver disease. *Liver Int* 2014; **34**: 235-242 [PMID: 23834275 DOI: 10.1111/liv.12242]
100 **Bhala N**, Angulo P, van der Poorten D, Lee E, Hui JM, Saracco G, Adams LA, Charatcharoenwitthaya P, Topping JH, Bugianesi E, Day CP, George J. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. *Hepatology* 2011; **54**: 1208-1216 [PMID: 21688282 DOI: 10.1002/hep.24491]
101 **Stepanova M**, Rafiq N, Makhlouf H, Agrawal R, Kaur I, Younoszai Z, McCullough A, Goodman Z, Younossi ZM. Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). *Dig Dis Sci* 2013; **58**: 3017-3023 [PMID: 23775317 DOI: 10.1007/s10620-013-2743-5]
102 **Younossi ZM**, Otgonsuren M, Venkatesan C, Mishra A. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. *Metabolism* 2013; **62**: 352-360 [PMID: 22999011 DOI: 10.1016/j.metabol.2012.08.005]
103 **Stepanova M**, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. *Gut* 2010; **59**: 1410-1415 [PMID: 20660697 DOI: 10.1136/gut.2010.213553]
104 **Nakanishi N**, Yoshida H, Nakamura K, Suzuki K, Tatara K. Alcohol consumption and risk for hypertension in middle-aged Japanese men. *J Hypertens* 2001; **19**: 851-855 [PMID: 11393666]
105 **Miller PM**, Anton RF, Egan BM, Basile J, Nguyen SA. Excessive alcohol consumption and hypertension: clinical implications of current research. *J Clin Hypertens* (Greenwich) 2005; **7**: 346-351 [PMID: 16088298]
106 **Seike N**, Noda M, Kadowaki T. Alcohol consumption and risk of type 2 diabetes mellitus in Japanese: a systematic review. *Asia Pac J Clin Nutr* 2008; **17**: 545-551 [PMID: 19114388]
107 **Van de Wiel A**. The effect of alcohol on postprandial and fasting triglycerides. *Int J Vasc Med* 2012; **2012**: 862504 [PMID: 21961068 DOI: 10.1155/2012/862504]
108 **Okanoue T**, Umemura A, Yasui K, Itoh Y. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in Japan. *J Gastroenterol Hepatol* 2011; **26** Suppl 1: 153-162 [PMID: 21199527 DOI: 10.1111/j.1440-1746.2010.06547.x]
109 **Toshikuni N**, Fukumura A, Hayashi N, Nomura T, Tsuchishima M, Arisawa T, Tsutsumi M. Comparison of the relationships of alcoholic and nonalcoholic fatty liver with hypertension, diabetes mellitus, and dyslipidemia. *J Clin Biochem Nutr* 2013; **52**: 82-88 [PMID: 23341703 DOI: 10.3164/jcbn.12-55]
110 **Djoussé L**, Ellison RC, Beiser A, Scaramucci A, D'Agostino RB, Wolf PA. Alcohol consumption and risk of ischemic stroke: The Framingham Study. *Stroke* 2002; **33**: 907-912 [PMID: 11935035]
111 **Lucas DL**, Brown RA, Wassef M, Giles TD. Alcohol and the cardiovascular system: research challenges and opportunities. *J Am Coll Cardiol* 2005; **45**: 1916-1924 [PMID: 15963387 DOI: 10.1016/j.jacc.2005.02.075]
112 **Hvidtfeldt UA**, Frederiksen ME, Thygesen LC, Kamper-Jørgensen M, Becker U, Grønbaek M. Incidence of cardiovascular and cerebrovascular disease in Danish men and women with a prolonged heavy alcohol intake. *Alcohol Clin Exp Res* 2008; **32**: 1920-1924 [PMID: 18715276 DOI: 10.1111/j.1530-0277.2008.00776.x]
113 **Armstrong MJ**, Adams LA, Canbay A, Syn WK. Extrahepatic complications of nonalcoholic fatty liver disease. *Hepatology* 2014; **59**: 1174-1197 [PMID: 24002776 DOI: 10.1002/hep.26717]
114 **Scoccianti C**, Straif K, Romieu I. Recent evidence on alcohol and cancer epidemiology. *Future Oncol* 2013; **9**: 1315-1322 [PMID: 23980679 DOI: 10.2217/fon.13.94]
115 **White DL**, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin Gastroenterol Hepatol* 2012; **10**: 1342-1359.e2 [PMID: 23041539 DOI: 10.1016/j.cgh.2012.10.001]
116 **Hashimoto E**, Taniai M, Kaneda H, Tokushige K, Hasegawa K, Okuda H, Shiratori K, Takasaki K. Comparison of hepatocellular carcinoma patients with alcoholic liver disease and nonalcoholic steatohepatitis. *Alcohol Clin Exp Res* 2004;

28: 164S-168S [PMID: 15318106]
117 **Kawada N**, Imanaka K, Kawaguchi T, Tamai C, Ishihara R, Matsunaga T, Gotoh K, Yamada T, Tomita Y. Hepatocellular carcinoma arising from non-cirrhotic nonalcoholic steatohepatitis. *J Gastroenterol* 2009; **44**: 1190-1194 [PMID: 19672551 DOI: 10.1007/s00535-009-0112-0]
118 **Ertle J**, Dechêne A, Sowa JP, Penndorf V, Herzer K, Kaiser G, Schlaak JF, Gerken G, Syn WK, Canbay A. Non-alcoholic fatty liver disease progresses to hepatocellular carcinoma in the absence of apparent cirrhosis. *Int J Cancer* 2011; **128**: 2436-2443 [PMID: 21128245 DOI: 10.1002/ijc.25797]
119 **Reddy SK**, Steel JL, Chen HW, DeMateo DJ, Cardinal J, Behari J, Humar A, Marsh JW, Geller DA, Tsung A. Outcomes of curative treatment for hepatocellular cancer in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. *Hepatology* 2012; **55**: 1809-1819 [PMID: 22183968 DOI: 10.1002/hep.25536]
120 **Kim SK**, Marusawa H, Eso Y, Nishikawa H, Ueda Y, Kita R, Kimura T, Chiba T, Osaki Y, Kudo M. Clinical characteristics of non-B non-C hepatocellular carcinoma: a single-center retrospective study. *Digestion* 2011; **84** Suppl 1: 43-49 [PMID: 22156485 DOI: 10.1159/000333212]
121 **Sanyal AJ**, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, Shiffman ML, Heuman D, Coterrell A, Fisher RA, Contos MJ, Mills AS. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. *Hepatology* 2006; **43**: 682-689 [PMID: 16502396 DOI: 10.1002/hep.21103]
122 **Wiegand J**, Kühne M, Pradat P, Mössner J, Trepo C, Tillmann HL. Different patterns of decompensation in patients with alcoholic vs. non-alcoholic liver cirrhosis. *Aliment Pharmacol Ther* 2012; **35**: 1443-1450 [PMID: 22530565 DOI: 10.1111/j.1365-2036.2012.05108.x]
123 **Xie YD**, Feng B, Gao Y, Wei L. Effect of abstinence from alcohol on survival of patients with alcoholic cirrhosis: A systematic review and meta-analysis. *Hepatol Res* 2013 Apr 11; Epub ahead of print [PMID: 23607793 DOI: 10.1111/hepr.12131]
124 **Yatsuji S**, Hashimoto E, Tobari M, Taniai M, Tokushige K, Shiratori K. Clinical features and outcomes of cirrhosis due to non-alcoholic steatohepatitis compared with cirrhosis caused by chronic hepatitis C. *J Gastroenterol Hepatol* 2009; **24**: 248-254 [PMID: 19032450 DOI: 10.1111/j.1440-1746.2008.05640.x]
125 **Bhagat V**, Mindikoglu AL, Nudo CG, Schiff ER, Tzakis A, Regev A. Outcomes of liver transplantation in patients with cirrhosis due to nonalcoholic steatohepatitis versus patients with cirrhosis due to alcoholic liver disease. *Liver Transpl* 2009; **15**: 1814-1820 [PMID: 19938128 DOI: 10.1002/lt.21927]
126 **Sotiropoulos GC**, Beckebaum S, Lang H, Frilling A, Molmenti EP, Cicinnati VR, Saner FH, Erim Y, Baba HA, Malagó M, Broelsch CE. Single-center experience on liver transplantation for hepatocellular carcinoma arising in alcoholic cirrhosis: results and ethical issues. *Eur Surg Res* 2008; **40**: 7-13 [PMID: 17717419 DOI: 10.1159/000107615]
127 **Afzali A**, Berry K, Ioannou GN. Excellent posttransplant survival for patients with nonalcoholic steatohepatitis in the United States. *Liver Transpl* 2012; **18**: 29-37 [PMID: 21932374 DOI: 10.1002/lt.22435]
128 **Trimble G**, Zheng L, Mishra A, Kalwaney S, Mir HM, Younossi ZM. Mortality associated with alcohol-related liver disease. *Aliment Pharmacol Ther* 2013; **38**: 596-602 [PMID: 23889765 DOI: 10.1111/apt.12432]
129 **Rafiq N**, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, Younossi ZM. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol* 2009; **7**: 234-238 [PMID: 19049831 DOI: 10.1016/j.cgh.2008.11.005]
130 **Adams LA**, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113-121 [PMID: 16012941]
131 **Ong JP**, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *J Hepatol* 2008; **49**: 608-612 [PMID: 18682312 DOI: 10.1016/j.jhep.2008.06.018]
132 **Adams LA**, Harmsen S, St Sauver JL, Charatcharoenwitthaya P, Enders FB, Therneau T, Angulo P. Nonalcoholic fatty liver disease increases risk of death among patients with diabetes: a community-based cohort study. *Am J Gastroenterol* 2010; **105**: 1567-1573 [PMID: 20145609 DOI: 10.1038/ajg.2010.18]
133 **Treeprasertsuk S**, Björnsson E, Enders F, Suwanwalaikorn S, Lindor KD. NAFLD fibrosis score: a prognostic predictor for mortality and liver complications among NAFLD patients. *World J Gastroenterol* 2013; **19**: 1219-1229 [PMID: 23482703 DOI: 10.3748/wjg.v19.i8.1219]

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