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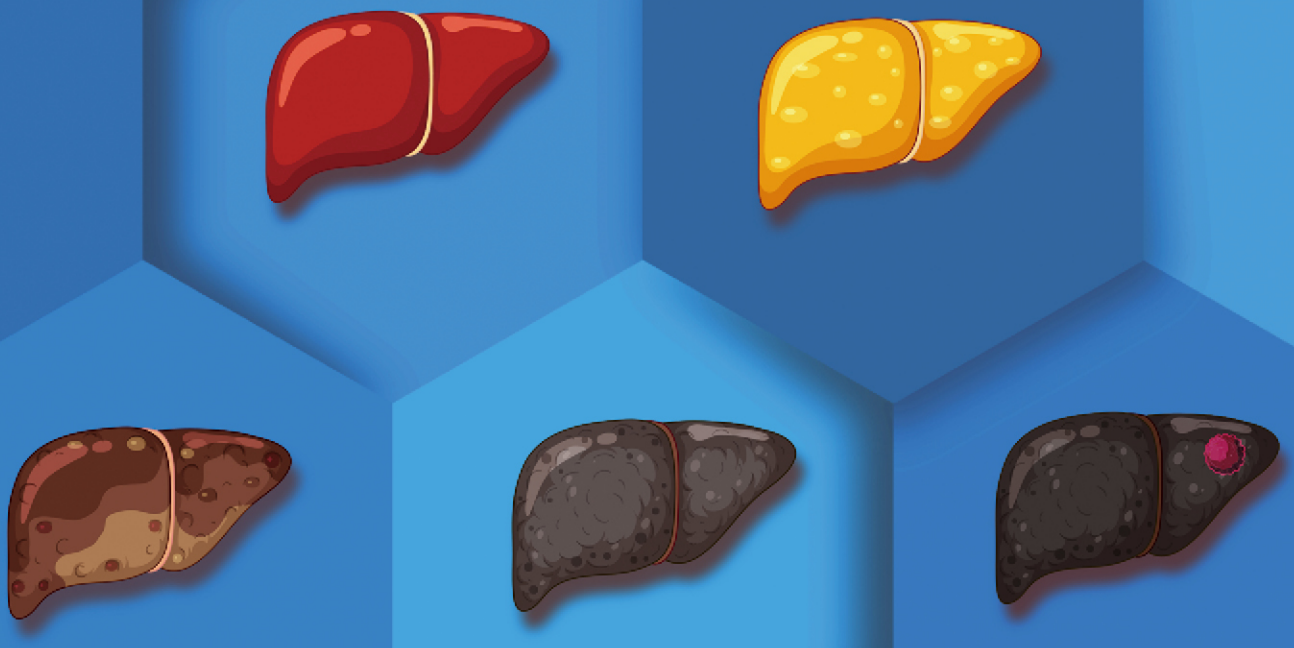

KASL 2025 MASLD clinical practice guidelines

Prognostication of MASLD

Epidemiology of MASLD

Precision medicine and MASH

Microbiome-centered therapies for MASLD

KASL

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KASL clinical practice guidelines for the management of metabolic dysfunction-associated steatotic liver disease 2025

Won Sohn[1,*], Young-Sun Lee[2,*], Soon Sun Kim[3,*], Jung Hee Kim[4,*], Young-Joo Jin[5,*], Gi-Ae Kim[6], Pil Soo Sung[7], Jeong-Ju Yoo[8], Young Chang[9], Eun Joo Lee[10], Hye Won Lee[11], Miyoung Choi[12], Su Jong Yu[13], Young Kul Jung[14], and Byoung Kuk Jang[15] on behalf of The Korean Association for the Study of the Liver (KASL)

[1]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; [2]Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul; [3]Department of Internal Medicine, Ajou University School of Medicine, Suwon; [4]Department of Internal Medicine, Dongtan Sacred Heart Hospital, Hallym University School of Medicine, Hwaseong; [5]Department of Internal Medicine, Inha University Hospital, Inha University School of Medicine, Incheon; [6]Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul; [7]Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul; [8]Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon; [9]Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Seoul; [10]Department of Pediatrics, Severance Hospital, Yonsei University College of Medicine, Seoul; [11]Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul; [12]Clinical Evidence Research, National Evidence-Based Healthcare Collaborating Agency, Seoul; [13]Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul; [14]Department of Internal Medicine, Korea University Ansan Hospital, Korea University College of Medicine, Ansan; [15]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea

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PREAMBLE

Purpose and scope

Nonalcoholic fatty liver disease (NAFLD) is defined as excessive fat accumulation in the liver in the absence of significant alcohol consumption. Recently, a novel concept of fatty liver disease (FLD) has emerged. When the term 'nonalcoholic' was first introduced, the disease identity of NAFLD was based on the exclusion of other etiologies for chronic liver disease. However, the characteristics of NAFLD have gradually been established, as it is closely

Corresponding author : Byoung Kuk Jang
Department of Internal Medicine, Keimyung University College of Medicine, 1035 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Korea
Tel: +82-53-258-7720, Fax: +82-53-258-4343, E–mail: jangha106@gmail.com
https://orcid.org/0000-0002-8950-0866

Young Kul Jung
Department of Internal Medicine, Korea University College of Medicine, 123 Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea
Tel: +82-31-412-7623, Fax: +82-31-412-5582, E-mail: 93cool@hanmail.net
https://orcid.org/0000-0002-6566-1382

*W Sohn, YS Lee, SS Kim, JH Kim, and YJ Jin contributed equally as co-first authors.

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associated with metabolic dysfunction such as obesity, insulin resistance, diabetes mellitus, hypertension, and dyslipidemia. The paradigm shift in FLD has transitioned from NAFLD to metabolic dysfunction-associated steatotic liver disease (MASLD), which requires the presence of at least one metabolic dysfunction.

Therefore, it is necessary to clarify the definition of MASLD and delineate the similarities and differences between NAFLD and MASLD. Moreover, resmetirom, an oral thyroid hormone receptor-beta (THR-β) agonist, demonstrated successful treatment outcomes for metabolic dysfunction-associated steatohepatitis (MASH) in a phase III clinical trial. Resmetirom was approved in March 2024 in the United States (US) as a treatment for MASH. It is necessary to share the knowledge for the clinical evidence and use of resmetirom for MASH. This guideline aimed to clarify the concept and clinical manifestations of MASLD and describe the clinical use and perspective of new pharmacologic therapy for MASH. Therefore, we reviewed Korean and international studies to prepare appropriate guidelines based on evidence, to reflect domestic conditions as much as possible. While the '2021 Korean Association for the Study of the Liver (KASL) Clinical Practice Guidelines for the Management of NAFLD' was completely revised, this guideline has been substantially amended to incorporate recent advances and updated recommendations on 11 clinical issues requiring updates in medical information. This guideline includes the Korean nomenclature, definition, diagnostic criteria, clinical manifestation, and prognosis of MASLD. It also shares updates on the drugs approved for MASH treatment and definition and diagnostic criteria of MASLD in pediatrics. There is a continuity between '2021 KASL Clinical Practice Guidelines for the Management of NAFLD' and the present guideline. We refer to the '2021 KASL Clinical Practice Guidelines for the Management of NAFLD' for the issues not included in this guideline. Those issues are risk factors including genetic factors, diagnostic methods, HCC surveillance, prevention of HCC, lifestyle modification, and surgical treatment.

These guidelines have been developed through reviewing medical evidence by experts to provide a practical reference for the treatment, research, and education of MASLD. They are not absolute standards for treatment, and the best choice of practice for individual patients may vary depending on their specific circumstances. In cases where related studies on clinically essential issues are lacking, we tried to present consensus opinions from experts. If relevant evidence based on new research results is accumulated in the future, these guidelines can be revised and supplemented. The guidelines cannot be modified, transformed, or reproduced without permission.

Target population

The target population of these guidelines includes adults, adolescents, and pediatric patients with MASLD.

Intended users

The following guidelines aim to provide clinical information useful for the decision-making of healthcare providers involved in the diagnosis and treatment of patients with MASLD and to raise awareness of MASLD among them, ultimately reducing morbidity and mortality and increasing the quality of life for patients with MASLD. In addition, these guidelines are intended to provide specific and practical information to resident physicians, practitioners, and trainers.

Abbreviations:

AASLD, American Association for the Study of Liver Diseases; AGREE II, Appraisal of Guidelines for Research and Evaluation II; ALD, alcohol-related liver disease; BMI, body mass index; CAP, controlled attenuation parameter; CI, confidence interval; CVD, cardiovascular diseases; EASL, European Association for the Study of the Liver; FASN, fatty acid synthase; FDA, Food and Drug Administration; FGF, fibroblast growth factor; FIB-4, fibrosis-4; FLI, fatty liver index; GLP-1, glucagon-like peptide-1; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; KASL, Korean Association for the Study of the Liver; LDL-C, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MASL, metabolic dysfunction-associated steatotic liver; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with increased alcohol consumption; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NAFL, nonalcoholic fatty liver; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Insurance Service; PPAR-γ, peroxisome proliferator-activated receptor-gamma; SCD1, stearoyl-CoA desaturase 1; SCORE2, systematic coronary risk evaluation 2; SGLT2, sodium-glucose cotransporter 2; SLD, steatotic liver disease; T2DM, type 2 diabetes mellitus; TE, transient elastography; THR-β, thyroid hormone receptor-beta; WHO, World Health Organization

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Guideline development group, process, and funding source

The Clinical Practice Guideline Committee for the Management of MASLD (hereafter referred to as 'the Committee') was organized in accordance with proposals approved by the KASL Board of Executives. The committee consists of 13 hepatologists, one pediatrician specializing in hepatology, and one methodology expert (Supplementary Table 1). The KASL paid all expenses, and the financial support did not affect the independence of the guideline contents. Each member of the committee collected and analyzed relevant evidence from their respective field and wrote the manuscript. The timeline of the guideline development process is shown in Supplementary Table 2. Conflicts of interest among the members are summarized in Supplementary Table 3.

Literature search for evidence collection

The committee collected relevant Korean and international literature through databases, including PubMed, MEDLINE, KoreaMed, KMBASE, RISS, and KISS, and analyzed them to establish guidelines based on the latest research and evidence. Only Korean and English literature was searched, and the search terms included 'nonalcoholic fatty liver disease' (NAFLD), 'metabolic dysfunction-associated fatty liver disease' (MAFLD), and 'metabolic dysfunction-associated steatotic liver disease' (MASLD).

Levels of evidence and grades of recommendations

The literature collected for evidence was analyzed through systematic review, and the levels of evidence were classified using the modified grading of recommendations, assessment, development, and evaluation (GRADE) system (Table 1).[1-3] They were categorized based on the possibility of changes in the assessment through further research as follows: high (A), with the lowest possibility; moderate (B), with certain possibility; and low (C), with the highest possibility. Specifically, depending on the type of study, randomized controlled trials start at a high level of evidence (A), and observational studies start at a low level of evidence (C). Considering factors affecting the study quality, the evidence level was raised or lowered further.[2] The strength of recommendation was suggested to be either strong (1) or weak (2), according to the GRADE system.[4] It was determined based on the clinical effects of recommendation, patient receptivity, and socioeconomic aspects, as well as the level of evidence. For example, a strong recommendation indicates that interventions could be applied in most patients with solid certainty regarding a greater possibility of desirable effects, high-quality evidence, presumed patient-important outcomes, cost-effectiveness, preference, and compliance. A weak recommendation indicates a suggestion made with less certainty, which could be considered favorable for many patients. Alternative interventions could be chosen for 'weak recom-

Table 1. GRADE (Grading of Recommendation, Assessment, Development, and Evaluation) system

	Criteria	
Quality of Evidence		
High quality (A)	Further research is very unlikely to change our confidence in the estimate of effect.	Randomized trials without important limitations
Moderate quality (B)	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	Randomized trials with important limitations or observational studies with special strengths
Low quality (C)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	Observational studies without special strengths or important limitations
Strength of Recommendation		
Strong (1)	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.	
Weak (2)	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost, or resource consumption.	

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mendations' according to the preferences of patients or medical practitioners.

List of key questions

The Clinical Practice Guideline Committee for the Management of MASLD selected the following key questions and presented evidence and recommendations for them.

1. What is the evolution of FLD?
2. What is the Korean nomenclature of MASLD?
3. What are the definition and diagnostic criteria of MASLD?
4. What are the prevalence and incidence of MASLD?
5. What is the risk of cardiovascular disease in MASLD?
6. What is the risk of hepatocellular carcinoma (HCC) in MASLD?
7. What is the risk of extrahepatic malignancy in MASLD?
8. What is the risk of liver fibrosis and cirrhosis in MASLD?
9. What are the all-cause mortality and liver-related mortality in MASLD?
10. What is the pharmacologic therapy for MASH?
11. What are the definition and diagnostic criteria in pediatric and adolescent patients with MASLD?

Internal and external review and approval process

Manuscripts and recommendations prepared by each member were reviewed for content integrity and validity during several committee meetings, and the quality of the guidelines was evaluated using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) criteria. The recommendations were assessed and revised based on the critical review by the Delphi Committee, consisting of nine experts in the field of hepatology belonging to the KASL (Supplementary Table 4). The guidelines were reviewed at a meeting of an external review board comprising six specialists in the field of hepatology and at a symposium open to all KASL members and the public, following which they were further modified. The Board of Executives of KASL endorsed the final manuscript.

Release of the guideline and plan for updates

The KASL Clinical Practice Guideline for the management of MASLD will be released at the Liver Week 2025 (May 29, 2025). The Korean version of the guideline is available on the KASL website (http://www.kasl.org). The KASL plans to update the guidelines when significant new evidence emerges, and revisions are deemed necessary to enhance Korea's national health.

NOMENCLATURE

Evolution of the nomenclature

Early period of fatty liver

Fatty liver refers to fat accumulation in hepatocytes caused by various factors. Addison of the United Kingdom named the condition 'fatty liver' in 1836 after observing fat accumulation in the livers of patients with excessive alcohol consumption.[5] In 1857, Budd reported that fatty liver development was associated with low physical activity and excessive fat intake. He observed hepatomegaly in these patients, with fat accumulation in hepatocytes, but noted no specific symptoms caused by this condition.[6] Later, several studies revealed that the development of fatty liver is strongly associated with obesity and diabetes.[7,8]

Period of NAFLD

In 1979, American clinicians Adler and Schaffner introduced the term 'fatty liver hepatitis' to describe an FLD associated with diabetes and obesity, characterized by hepatic inflammation and fibrosis, but not related to alcohol consumption.[9] In 1980, Ludwig et al. named the condition 'nonalcoholic steatohepatitis' (NASH) to describe FLD with histological features of hepatic inflammation and varying degrees of fibrosis in patients without a history of alcohol consumption.[10] Histological features included fat accumulation, lobular hepatitis, inflammatory infiltrates, and Mallory bodies, accompanied by varying degrees of hepatic fibrosis, which could progress to liver cirrhosis caused by steatohepatitis.[11] The term NAFLD was first introduced in 1986 in a review article by Schaffner and Thaler.[12] It has been used for decades as an umbrella term encompassing a wide spectrum of conditions, ranging from simple steatosis

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to steatohepatitis and cirrhosis.

Need for new terminology for the FLD and its development

Since the term 'NAFLD' was proposed, accumulating knowledge about the causes and mechanisms of the disease has established a strong association between its development and 'metabolic dysfunction,' including obesity, insulin resistance, diabetes, hypertension, and dyslipidemia. However, the term 'NAFLD' has been criticized for being a diagnosis of exclusion, failing to reflect the underlying cause of the disease accurately. Additionally, the inclusion of 'non-' in the disease name has been criticized for potentially diminishing the perceived significance of the condition.[13] Furthermore, it has been overlooked that, even in the presence of other chronic diseases, fatty liver can develop or worsen owing to metabolic dysfunction. Eslam et al. proposed the term 'metabolic dysfunction-associated fatty liver disease' (MAFLD) in 2020 to address these issues.[14] However, concerns have been raised that MAFLD includes patients with chronic liver diseases of other etiologies and alcohol-related liver disease, making it challenging to develop disease-specific biomarkers. Additionally, it does not encompass the concept of steatohepatitis, which may limit its consideration of implications for new drug development.[15,16] Discussions on a new concept of FLD have been conducted to overcome these issues and incorporate metabolic dysfunction, the core mechanism of disease development, into the disease name. In 2023, members of multinational liver societies, including the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), led discussions to establish a new terminology for FLD. Using the Delphi method, which involved online surveys and hybrid meetings, a panel of 236 experts from 56 countries worldwide reached a consensus on adopting the terms 'steatotic liver disease'(SLD), with MASLD as a subtype.[17,18]

Korean nomenclature

As explained earlier, the new concept of FLD has led to changes in its English nomenclature. Consequently, there is a need to establish the Korean nomenclature for this new concept.

The Korean term for NAFLD

Fat accumulation can occur without excessive alcohol consumption, and this condition is defined as '비알코올지방간질환' (NAFLD), a term that has been used for the past several decades. NAFLD is primarily defined based on histological findings. It includes '비알코올지방간' (nonalcoholic fatty liver, NAFL), characterized by simple fat accumulation in the liver, and '비알코올지방간염' (NASH), which involves not only fat accumulation but also lobular inflammation and hepatocyte ballooning and degeneration. The development of NASH can lead to liver fibrosis and cirrhosis, which can result in HCC and cirrhosis-related complications. The above Korean term has been used for the disease spectrum of NAFLD to this day.

Establishment of the Korean nomenclature for MASLD

With the proposal of a new nomenclature for FLD, discussions on an appropriate Korean designation have become necessary. Although the AASLD and the EASL proposed using the term 'steatotic' instead of 'fatty', both terms translate into the same Korean word, '지방'.[17,18] In December 2023, the KASL recognized the importance of internationally unified and accurate terminology and approved the organization of the 'NAFLD Nomenclature Revision Consensus Task Force'. In February 2024, the 'NAFLD Nomenclature Revision Consensus Task Force' under the KASL was established, initiating work to define new terminology for FLD and revise it into Korean.[19] The NAFLD Nomenclature Revision Consensus Task Force, composed of eight experienced liver specialists in Korea, aimed to revise the terminology to reflect the nature of FLD accurately and improve patients' understanding of their condition. As a part of this effort, the NAFLD Nomenclature Revision Consensus Task Force first conducted a survey to gather opinions from the KASL members. The survey results showed that the terms 'FLD' and 'SLD' received the most responses for being uniformly named as '지방간질환' in Korean. For the Korean names 'MAFLD' and 'MASLD,' the survey responses indicated a preference for uniformly naming them as '대사이상지방간질환' or '대사이상관련지방간질환'.[19] After extensive discussions and consideration of the survey results, the NAFLD Nomenclature Revision Consensus Task Force decided to term SLD in Korean the same as the existing term for 'FLD' that is, as '지방간질환' despite the differences in

their English terminologies. Accordingly, the Korean names for MAFLD and MASLD were also naturally decided to be the same. Considering the above, the NAFLD Nomenclature Revision Consensus Task Force concluded that '대사이상지방간질환' is the most appropriate Korean term for MAFLD and MASLD, and that '대사이상지방간질환' and '대사이상관련지방간질환' carry the same medical meaning. However, the former was deemed more appropriate as it is easier to communicate in real practice and explain to Korean patients.[19] Additionally, considering that MASLD is very common in Korea, affecting approximately 25–30% of the population, it was determined that a shorter name would be easier to apply than a longer one. Lastly, the NAFLD Nomenclature Revision Consensus Task Force concluded that while the English names can be easily communicated using the abbreviations MAFLD or MASLD, the absence of such abbreviations in Korean makes the more concise term '대사이상지방간질환' more suitable as the Korean nomenclature. Thus, the KASL coined the Korean terms for MAFLD and MASLD (Fig. 1).

[Summary]

- A new concept of FLD, MASLD, has been recently introduced to emphasize metabolic dysfunction as the pathophysiological mechanism of NAFLD.
- The Korean term for MASLD is '대사이상지방간질환'.

DEFINITION AND DIAGNOSIS

NAFLD

NAFLD is defined as a condition characterized by hepatic fat accumulation on pathological, radiological, or biochemical examinations in the absence of secondary causes such as significant alcohol consumption, drug-induced liver injury, or viral hepatitis.[20] NAFLD encompasses the diagnostic categories of NAFL, NASH, and NAFLD-related cirrhosis. Although the upper limit of significant alcohol consumption varies between studies, ranging from 10 to 40 g of pure alcohol per day, making it difficult to provide a definitive threshold, the '2021 KASL Clinical Practice Guideline for NAFLD' defines significant alcohol consumption as >210 g/week for men, and >140 g/week for women.[21] Diagnosing NAFLD requires the exclusion of other chronic liver diseases, including significant alcohol consumption.

MAFLD

In 2020, MAFLD was proposed as 'a diagnosis when hepatic steatosis is confirmed by pathological, radiological, or biochemical examination, along with the presence of overweight/obesity (body mass index [BMI] ≥23 kg/m² for Asians and ≥25 kg/m² for Western populations), type 2 diabetes mellitus (T2DM), or metabolic abnormalities'. Unlike NAFLD, the diagnosis of MAFLD does not require the exclusion of excessive alcohol consumption and can be

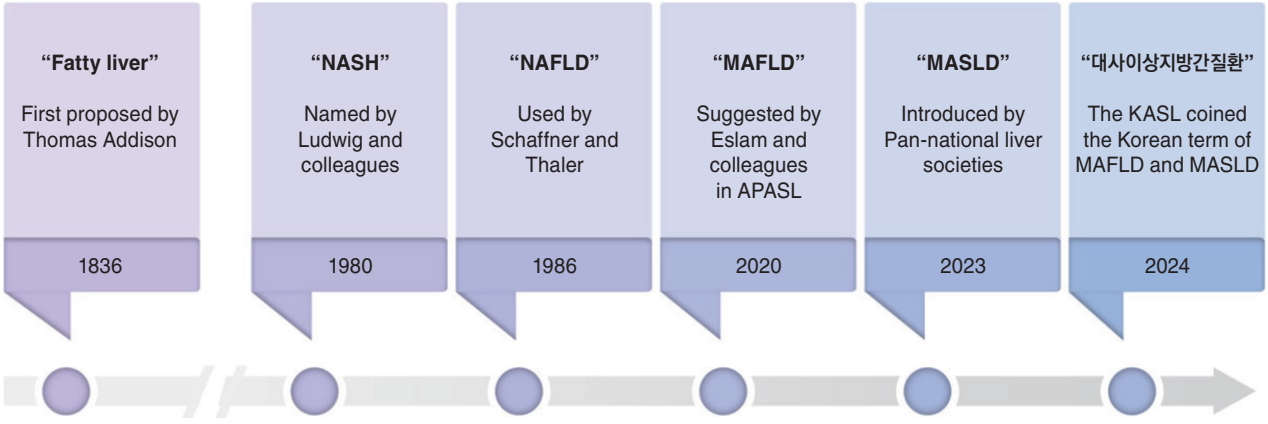

Figure 1. Evolution and nomenclature of fatty liver disease. NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; APASL, Asian Pacific Association for the Study of the Liver; MASLD, metabolic dysfunction-associated steatotic liver disease; KASL, Korean Association for the Study for the Liver.

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made regardless of the presence of other chronic liver diseases. Additionally, it was suggested that the disease progression of MAFLD be described by activity grade and fibrosis stage rather than a dichotomous classification of steatohepatitis or simple steatosis.[14,22] However, limitations of MAFLD include the lack of input from various stakeholders, such as patient advocacy groups, during its formulation; the continued use of the term 'fatty'; inclusion of metabolic risk factors such as homeostatic model assessment for insulin resistance (HOMA-IR) and high-sensitivity C-reactive protein (hs-CRP), which are not frequently used in clinical practice; and exclusion of the concept of steatohepatitis, making it difficult to apply prior clinical trial results of NASH treatments.

MASLD

The most recently proposed term, MASLD, is defined as the 'presence of hepatic steatosis along with at least one cardiometabolic risk factor'.[17,18] Cardiometabolic risk factors are identified when at least one of the following five conditions is present: (1) BMI ≥23 kg/m² in Koreans and Asians or ≥25 kg/m² in Western populations; or a waist circumference ≥90 cm for men and ≥85 cm for women in Korea, or ≥94 cm for men and ≥80 cm for women according to the World Health Organization (WHO),[23,24] (2) fasting blood glucose ≥100 mg/dL, postprandial 2-h blood glucose ≥140 mg/dL, HbA1c ≥5.7%, or a diagnosis of T2DM or antidiabetic medication use; (3) blood pressure ≥130/85 mmHg or antihypertensive medication use; (4) triglycerides ≥150 mg/dL or lipid-lowering medication use; or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL for men and <50 mg/dL for women, or lipid-lowering medication use.[25] The WHO has proposed the criteria for abdominal obesity in the Asia-Pacific region as a waist circumference ≥90 cm for men and ≥80 cm for women. However, considering the average waist circumference of Korean adults, the criteria in Korea are set at ≥90 cm for men and ≥85 cm for women. As the

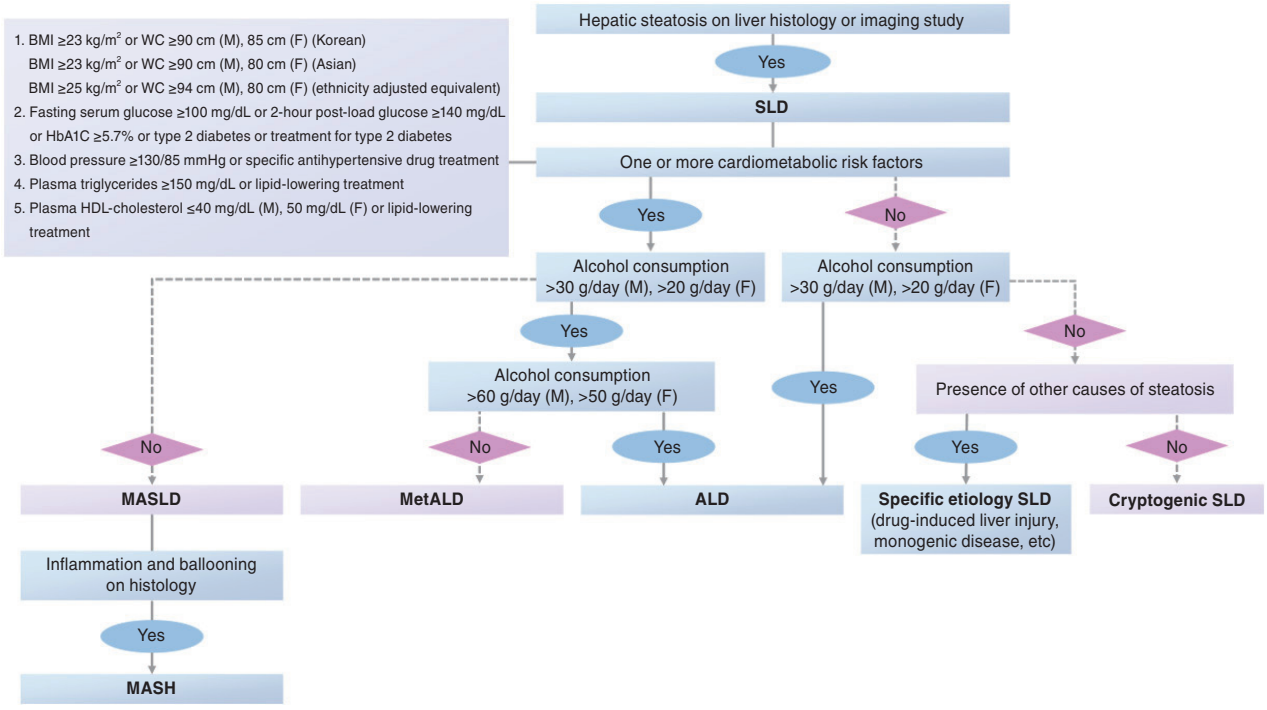

Figure 2. Diagnostic algorithm for MASLD. The specific etiology of SLD includes drug-induced liver injury (e.g., corticosteroids, tamoxifen, amiodarone, irinotecan, methotrexate, lomitapide, valproate, and 5-fluorouracil), monogenic diseases (e.g., lysosomal acid lipase deficiency, Wilson's disease, hypobetalipoproteinemia, inborn errors of metabolism), and other conditions such as HCV genotype 3 infection, malnutrition, celiac disease, HIV, and environmental exposure to agents associated with steatosis (e.g., hydrocarbon inhalation). BMI, body mass index; M, male; F, female; WC, waist circumference; SLD, steatotic liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with increased alcohol consumption; ALD, alcohol-related liver disease; MASH, metabolic dysfunction-associated steatohepatitis.

diagnostic criteria for abdominal obesity vary by country and ethnicity, it is necessary to take these differences into account and apply them appropriately.[24,26] The term MASLD encompasses various disease conditions, including metabolic dysfunction-associated steatotic liver (MASL), MASH, and cirrhosis. MASLD is classified as a subtype of the newly proposed category of SLD. In addition to MASLD, SLD includes MASLD with increased alcohol consumption (MetALD), which refers to moderate alcohol intake, defined as 30–60 g/day for men and 20–50 g/day for women; alcohol-related liver disease (ALD), associated with either significant alcohol consumption in the absence of cardiometabolic risk factors or excessive alcohol consumption in the presence of cardiometabolic risk factor(s); specific etiology SLD caused by drugs or monogenic disease; and cryptogenic SLD (Fig. 2).[17] Besides alcohol amount, binge drinking and the period of alcohol use would be considered to differentiate the diagnosis of MASLD, MetALD, and ALD. Since current drinking pattern may not fully reflect their past alcohol exposure, it is important to assess a more detailed history of alcohol use. However, there is a lack of evidence on binge drinking and the period of alcohol use to differentiate the diagnosis of MASLD, MetALD, and ALD. Further researches are needed to determine how drinking history and episodic heavy drinking should be considered in clinical practice. When MASLD coexists with another SLD subtype, the condition can be classified as a combination etiology.

Comparison of the definitions and diagnostic criteria of NAFLD, MAFLD, and MASLD

The definitions of NAFLD, MAFLD, and MASLD differ in terminology, diagnostic methods for hepatic steatosis, alcohol consumption thresholds, and diagnostic criteria (Table 2). NAFLD includes the terms ‘nonalcoholic’ and ‘fatty’ and diagnoses hepatic fat accumulation through blood tests, imaging, or histological examination. Diagnosis requires the absence of significant alcohol consumption (<30 g/day for men and <20 g/day for women). Cardiometabolic risk factors are not included in the diagnostic criteria. NAFLD is diagnosed by excluding other chronic liver diseases and causes of hepatic steatosis.

In contrast, MAFLD excludes the term ‘nonalcoholic’ and emphasizes ‘metabolic dysfunction’. Diagnosis of MAFLD can be made when hepatic steatosis is confirmed by blood tests (e.g., fatty liver index [FLI], hepatic steatosis index),[27,28] imaging, or histological examination, along with the presence of overweight/obesity, T2DM, or two or more metabolic risk factors. Unlike NAFLD or MASLD, MAFLD does not have an alcohol consumption threshold and does not require the exclusion of other causes of chronic liver

Table 2. Comparison of the definitions and diagnostic criteria of NAFLD, MAFLD, and MASLD

	NAFLD	MAFLD	MASLD
Term	Includes “nonalcoholic”, “fatty”	Excludes “nonalcoholic”, emphasizes “metabolic dysfunction”	Replaces “fatty” to “steatotic”, emphasizes “metabolic dysfunction”
Diagnosis of hepatic steatosis	Imaging studies or blood biomarkers or liver histology	Imaging studies or blood biomarkers or liver histology	Imaging studies or liver histology
Steatohepatitis	NASH	-	MASH
Amount of alcohol consumption	<30 g/day (M), 20 g/day (F)	Regardless of alcohol consumption	<30 g/day (M), 20 g/day (F)
Criteria for metabolic dysfunction	None	Overweight or obesity, Type 2 diabetes, or presence of ≥2 metabolic risk abnormalities	Presence of any of the cardiometabolic criteria
Inclusion of HOMA-IR, hs-CRP for metabolic risk factors	No	Yes	No
Other cause of steatosis	Exclusion	Inclusion	Exclusion

NAFLD, nonalcoholic fatty liver disease; MAFLD, metabolic dysfunction-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NASH, nonalcoholic steatohepatitis; MASH, metabolic dysfunction-associated steatohepatitis; M, male; F, female; HOMA-IR, homeostatic model assessment for insulin resistance; hs-CRP, high sensitivity C-reactive protein.

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disease or hepatic steatosis. Additionally, MAFLD differs from MASLD, as the former includes metabolic risk factors such as HOMA-IR and hs-CRP.

MASLD also emphasizes 'metabolic dysfunction' but differs from MAFLD by using the term 'steatotic' instead of 'fatty'. MASLD is diagnosed through imaging or histological examination when at least one cardiometabolic risk factor is present. It also differs from MAFLD, as significant alcohol consumption must be absent (<30 g/day for men and <20 g/day for women), and other causes of SLD must be excluded.

Concerns have been raised regarding whether findings from studies on patients with NAFLD can be directly applied to those with MASLD. In a French cohort of 2,187 patients diagnosed with NAFLD through liver biopsy, MASLD diagnostic criteria were also applied. The results showed a concordance rate of 98.4%, with only 1.6% of patients not meeting the MASLD criteria.[29] In a Swedish cohort study of 1,333 patients with NAFLD, 99.7% of them met the MASLD criteria. The overall survival rates and liver-related outcomes exhibited similar trends between the two groups.[30] An analysis of data from the National Health and Nutrition Examination Survey (NHANES) in the US reported a MASLD prevalence of 31.3%, with a concordance rate of 99% between NAFLD and MASLD.[31] In a Korean study analyzing 2,535 individuals who underwent magnetic resonance imaging proton density fat fraction (MRI-PDFF) at five health check-up centers, 992 individuals (39.1%) were diagnosed with SLD, 745 (29.4%) with MASLD, and 735 (29.0%) with NAFLD. Among those with MASLD, 94.5% (704/745) were also classified as having NAFLD. Similarly, 95.8% (704/735) of those with NAFLD were classified as having MASLD. The 31 patients who did not meet the MASLD criteria were all identified as having cryptogenic SLD.[32]

[Summary]

- MASLD is diagnosed when hepatic steatosis is confirmed by imaging or liver biopsy, with the presence of at least one cardiometabolic risk factor and non-significant alcohol consumption.
- Patients diagnosed with the MASLD criteria show a high concordance rate (>95%) with those diagnosed with NAFLD.

EPIDEMIOLOGY

Prevalence

In Korea, the prevalence of NAFLD diagnosed using ultrasonography was reported to be 25.2% in 2009, based on a study of 141,610 health check-up participants.[33] A systematic review including 61 studies conducted in Korea reported a 30.3% prevalence of NAFLD among 837,897 Korean individuals, with a 41.1% prevalence in men and 20.3% in women.[34] A meta-analysis of 237 studies conducted in Asia and published between 1999 and 2019 reported a 32.9% prevalence of NAFLD diagnosed using ultrasonography in Korea[35] and a global meta-analysis reported a 34.6% prevalence of NAFLD.[36] These findings suggest that the prevalence of NAFLD in Korea, Asia, and worldwide is relatively similar. When transient elastography (TE) was used to define fatty liver with a controlled attenuation parameter (CAP) score ≥250 dB/m, the prevalence of NAFLD was reported to be 42.9%.[37] A study using liver biopsy data from living liver donors in Korea reported a 51.4% NAFLD prevalence.[38] The prevalence of MAFLD diagnosed using ultrasonography was 33.9% among 6,775 health check-up participants from 13 institutions in Korea.[39] When fatty liver was defined as an FLI ≥30 among health check-up participants, the prevalence of MAFLD was 37.3%.[40]

The prevalence of MASLD varies depending on the study population, definition, and diagnostic methods. The prevalence of MASLD diagnosed using ultrasonography was found to be 33.5% among 7,918 health check-up participants in Korea.[41] When fatty liver was defined as ≥5% liver fat content on MRI-PDFF, the prevalence of MASLD among 2,535 health check-up participants from five institutions in Korea was 29.5%.[32] In the same population, the prevalence of NAFLD was 29.1%. In a single health screening center in Korea, when fatty liver was defined as ≥5% liver fat content on MRI-PDFF, the prevalence of MASLD was found to be 25.2%.[42] In the same cohort, the prevalence of MAFLD was 29.5%, and that of NAFLD was 25.9%. In 2009, a study of 9,775,066 health check-up participants found that when fatty liver was defined as an FLI ≥30, the prevalence of MASLD was 27.5%, with 39.5% in men and 17.4% in women.[43] In the same population, the prevalence of MAFLD was 36.1%, and that of NAFLD was 27.6%. It is

generally known that MASLD is more prevalent in men than in women; however, its prevalence tends to be higher in postmenopausal women.[44] A 2010 Korean study of 351,068 health check-up participants reported a MASLD prevalence of 47.2% when fatty liver was defined as an FLI ≥60.[45] In the Ansung–Ansan cohort of 9,497 participants, when fatty liver was defined as an FLI ≥30, the prevalence of MASLD was reported to be 38.3%.[46] When fatty liver is defined based on the FLI, there tends to be some variation in prevalence estimates, often indicating a higher incidence.

Incidence

The incidence of NAFLD in Korea has been increasing. A Korean study that followed 5,237 men for >4 years reported the incidence rate of NAFLD to be 74.1 cases per 1,000 person-years.[47] Among health check-up participants, when diagnosed using ultrasonography, the incidence rate was reported to be approximately 48.2 cases per 1,000 person-years (13.4–77.7 cases).[48-54] A meta-analysis of 237 studies from Asia, published between 1999 and 2019, reported an incidence rate of 45.1 cases per 1,000 person-years in Korea,[35] and a global meta-analysis reported an incidence rate of 60.2 cases per 1,000 person-years.[36] Studies on MASLD incidence remain limited, highlighting the need for further research to assess its incidence accurately. It is expected that the incidence will likely increase, similar to the trend observed for NAFLD.

[Summary]

- The prevalence and incidence of MASLD are expected to be similar to those of NAFLD.

CLINICAL MANIFESTATIONS AND PROGNOSIS

Patients with MASLD are at an increased risk of liver-related complications, including progression to liver fibrosis, cirrhosis, and HCC. In addition, they are more susceptible to cardiovascular diseases (CVD) and extrahepatic malignancies, contributing to an overall increase in mortality risk (Fig. 3).

CVD

MASLD has been shown to follow a natural history, including clinical outcomes and mortality rates comparable to those of NAFLD.[30,55] This has led to the proposition that previous research findings on NAFLD could be extended to MASLD.[56] Cohort studies diagnosing NAFLD based on histological or imaging criteria have consistently shown an increased incidence of CVD and related mortality compared to non-steatotic controls. However, some variations exist depending on the diagnostic method for hepatic steatosis, type of CVD, and adjustment factors used in the analysis.[57-59]

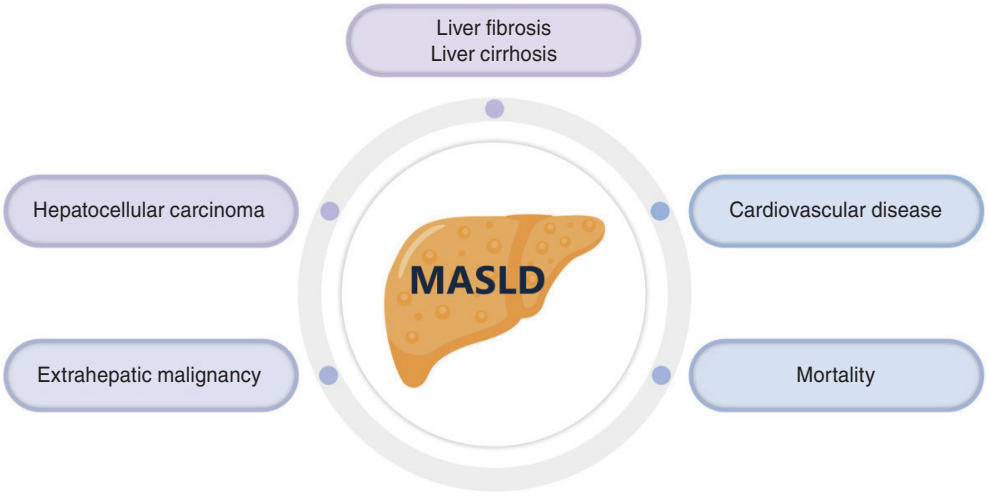

Figure 3. Clinical manifestations and prognosis of MASLD. MASLD, metabolic dysfunction-associated steatotic liver disease.

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In a Swedish study involving biopsy-proven patients with NAFLD followed for 13 years, the incidence of CVD was 24.3 cases per 1,000 person-years, while the CVD-related mortality rate was 7.2 deaths per 1,000 person-years. Notably, the risk of CVD-related mortality remained significantly elevated even after adjusting for confounding factors such as age, sex, diabetes, and obesity (hazard ratio [HR] 1.37, 95% confidence interval [CI] 1.27–1.48).[57] In a recent meta-analysis of 79 studies on NAFLD diagnosed through histological or imaging methods, the incidence of CVD was reported as 24.77 cases per 1,000 person-years, closely aligning with previous research findings. Additionally, the meta-analysis reported a CVD-related mortality rate of 4.5 deaths per 1,000 person-years.[59] Another meta-analysis comprising 36 studies on NAFLD further confirmed a significant elevation in the risk of CVD-related mortality (HR 1.30, 95% CI 1.08–1.56).[60]

Using data from the US NHANES, a 23-year longitudinal cohort study that defined hepatic steatosis via ultrasound demonstrated that individuals with MAFLD had a significantly increased risk of CVD-related mortality even after adjusting for age, sex, and other confounding factors (HR 1.33, 95% CI 1.22–1.44).[58] A cohort study based on national health screening data from the National Health Insurance Service (NHIS) in Korea, which defined MAFLD using an FLI ≥30, demonstrated that the incidence of CVD was 3.18 cases per 1,000 person-years and the CVD-related mortality rate was 0.47 deaths per 1,000 person-years. The study further confirmed a significant increase in the risk of CVD-related mortality (HR 1.46, 95% CI 1.41–1.52).[40]

In a 12-year observational study based on national health screening data from the NHIS in Korea, where MASLD was defined using an FLI ≥30, the incidence of CVD was 3.79 cases per 1,000 person-years, compared to 2.06 cases per 1,000 person-years in the control group. The CVD-related mortality rate was 0.8 deaths per 1,000 person-years in the MASLD group, while the control group had a rate of 0.5 deaths per 1,000 person-years. The risk of CVD-related mortality was significantly elevated in the MASLD group relative to the control group (HR 1.13, 95% CI 1.11–1.15).[43] Another study based on the NHIS in Korea, wherein MASLD was defined using an FLI ≥60 and followed for 9 years, reported an annual CVD incidence of 8.5 cases per 1,000 person-years, compared to 6.2 cases per 1,000 person-years in the control group.[45] Both studies demonstrated that the incidence of CVD was higher in individuals with MASLD than in non-steatotic controls. However, a recent 23-year follow-up study using data from the US NHANES, which defined hepatic steatosis using ultrasound, found that, even after adjusting for risk factors such as age and sex, the risk of CVD-related mortality in individuals with MASLD did not show a significant increase compared to the control group (HR 1.11, 95% CI 0.98–1.27). In contrast, the risk of CVD-related mortality was significantly increased in MAFLD when including viral hepatitis and alcohol-related liver disease (HR 1.13, 95% CI 1.01–1.27).[61]

A scoring system for predicting the risk of CVD in individuals with NAFLD has been validated. The Framingham Risk Score and Atherosclerotic CVD Risk Score, which use indicators such as age, sex, total cholesterol and high-density lipoprotein cholesterol levels, blood pressure, diabetes, and smoking status, have been shown to be applicable in predicting the 10-year risk of CVD in individuals with NAFLD.[62,63] The Systematic COronary Risk Evaluation 2 (SCORE2) model and the SCORE2-Older Persons model, developed in Europe, can be used to estimate the 10-year CVD risk in patients with NAFLD.[64] Recent studies suggesting minimal differences between the patient populations of NAFLD and MASLD imply that CVD risk prediction models developed for NAFLD may also be applicable to MASLD. However, further investigation is warranted to substantiate this hypothesis.

[Summary]

- The risk of CVD is increased in patients with MASLD, and CVD serves as a major cause of mortality in MASLD.

HCC

HCC is the third leading cause of cancer-related mortality worldwide, and the increasing prevalence of MASLD continues to contribute to the development of HCC significantly.[65] Consequently, further epidemiological research on the incidence of HCC within the framework of the evolving spectrum of SLD is essential.

In patients with NAFLD, the incidence of HCC is extremely low in the absence of progressive hepatic fibrosis (F0-2).[66] However, in patients with cirrhosis related to

NAFLD, the annual incidence of HCC exceeds 1.5%. Therefore, clinical suspicion of cirrhosis warrants surveillance for HCC.[66] A cohort study based on national health screening data from the NHIS in Korea found that the incidence of HCC was higher in patients with MAFLD compared to those without hepatic steatosis (0.37 cases per 1,000 person-years vs. 0.24 cases per 1,000 person-years). When stratified by the presence of other chronic liver diseases, MAFLD was not associated with HCC in patients with concurrent chronic liver conditions. In contrast, in patients without other chronic liver diseases, MAFLD emerged as an independent cause of HCC (adjusted HR 1.84, 95% CI 1.09–3.11).[67]

A study based on the NHIS in Korea, which followed participants for 13 years, found that the incidence of HCC was 0.24% in the non-MASLD group and 0.62% in the MASLD group. The age-standardized 5-year cumulative incidence of HCC was 0.09% in the non-MASLD group and 0.18% in the MASLD group.[68] According to an additional domestic study using data from the NHIS on individuals who underwent biennial health screenings, the incidence of HCC was significantly elevated in individuals with MASLD compared to those without MASLD, over a follow-up period exceeding 10 years (adjusted HR 2.94, 95% CI 2.68–3.21).[69] A domestic study using data from 29,060 hospital health check-up patients found that the annual incidence of HCC in individuals with MASLD was 0.18 cases per 1,000 person-years.[70] A study conducted in Taiwan, which followed 5,203,878.9 person-years of patients with SLD, identified 1,392 new cases of HCC, yielding an annual incidence rate of 26.8 cases per 100,000 person-years. Among these patients, the incidence of HCC in those with MASLD was higher, at 30.7 cases per 100,000 person-years.[71] In a study involving 220 patients with MASLD-related decompensated cirrhosis, 40 (18.2%) developed HCC during an average follow-up period of 3.2 years.[72]

[Summary]

- The risk of HCC is increased in patients with MASLD.

Extrahepatic malignancy

Patients with NAFLD exhibit a significantly higher prevalence of extrahepatic malignancies compared to control groups. A meta-analysis of 10 studies demonstrated that the presence of NAFLD is associated with an increased prevalence of extrahepatic malignancies.[73] NAFLD was associated with a 1.5- to 2-fold increase in the prevalence of gastrointestinal cancers, including esophageal, gastric, pancreatic, and colorectal cancers. Additionally, the prevalence of lung cancer, breast cancer, gynecological malignancies, and urological cancers increased by an average of 1.2–1.5 times in patients with NAFLD. A meta-analysis of 22 studies further demonstrated that NAFLD is associated with an increased risk of various extrahepatic cancers, including thyroid, pancreatic, gastrointestinal, urological, breast, and lung cancers. The risk ranged from a 1.3-fold increase (lung cancer: HR 1.25, 95% CI 1.11–1.40) to a 2.6-fold increase (thyroid cancer: HR 2.63, 95% CI 1.27–5.45.[74] In a study of 25,947 Koreans who underwent health check-ups in 2004, patients with hepatic steatosis showed a significantly higher incidence of overall malignancies compared to those without hepatic steatosis (HR 1.32, 95% CI 1.17–1.49).[75] Notably, men with NAFLD exhibited a significantly higher incidence of colorectal cancer, while women showed a markedly increased risk of breast cancer. A meta-analysis of 64 studies reported that the incidence of extrahepatic malignancies in patients with NAFLD was 10.58 cases per 1,000 person-years, with notably higher rates of uterine, breast, prostate, colorectal, and lung cancers.[76] However, among patients with NAFLD, the progression to liver fibrosis or cirrhosis was not associated with a further increase in the incidence of extrahepatic malignancies.[76]

MAFLD significantly contributes to an increased risk of extrahepatic malignancies. Analysis of data from the NHIS in Korea demonstrated that MAFLD is associated with an increased prevalence of 23 distinct extrahepatic malignancies. This risk was significantly amplified in individuals with multiple metabolic abnormalities compared to those with a single metabolic risk factor.[77] In an analysis involving 151,391 patients from China, MAFLD was found to elevate the risk of developing extrahepatic malignancies by 1.1 folds (HR 1.05, 95% CI 0.99–1.11), with a statistically significant increase observed in the incidence of thyroid, renal, prostate, and breast cancers.[78] Various studies have highlighted abdominal obesity, elevated BMI, T2DM, and the presence of multiple metabolic abnormalities as key risk factors for the development of extrahepatic malignancies.[79] To date, the prevalence and incidence of extrahepatic ma-

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lignancies in patients with MASLD have not been extensively studied. A recent Australian study reported that the incidence of various malignancies was twice as high in individuals with MASLD compared to those without it. Furthermore, patients with cirrhosis and T2DM were at an even greater risk of developing extrahepatic malignancies.[80] Although additional studies are warranted, the comparable clinical course of MASLD and the former definition of NAFLD suggest that the incidence of extrahepatic malignancies in MASLD is likely elevated relative to that in control populations (Fig. 4).

[Summary]

- The risk of extrahepatic malignancies is elevated in individuals with MASLD, with obesity and diabetes serving as prominent contributing factors.

Liver fibrosis and cirrhosis

While NAFL is typically associated with a favorable prognosis, some patients with NASH may develop advanced liver diseases, including cirrhosis and HCC. In particular, the presence of advanced fibrosis in NASH significantly increases the risk of complications such as cirrhosis and liver-related mortality.[20,81]

A meta-analysis of 151 studies published since 2000 reported that among overweight individuals with NAFLD, the prevalence of liver fibrosis (F1–4) was 46.6% (95% CI 26.6–67.7), that of advanced fibrosis (F3–4) was 6.7% (95% CI 4.4–10.0), and that of cirrhosis (F4) was 2.5% (95% CI 1.6–3.7). In overweight individuals with NASH, the prevalence was even higher, with the prevalence of liver fibrosis at 72.6% (95% CI 49.4–87.8), that of advanced fibrosis (F3–4) at 19.4% (95% CI 7.6–41.1), and that of cirrhosis (F4) at 1.7% (95% CI 0.4–6.6).[82] Another meta-analysis reported that among non-obese patients with NAFLD, 29.2% had significant liver fibrosis (≥F2), and 3.2% had cirrhosis.[83] Various cohort studies and meta-analyses following patients with NAFL and NASH have reported diverse rates of fibrosis progression. One study involving 55 patients with NAFLD reported a fibrosis progression rate of 27% over 3 years based on serial biopsies conducted at 3-year intervals.[84] In another study of 70 patients with biopsies performed at intervals of >1 year, the fibrosis progression rate was 29% over an average follow-up of 3.7 years.[85] A separate study of 108 patients who underwent serial biopsies reported an annual fibrosis progression rate of 0.08±0.25

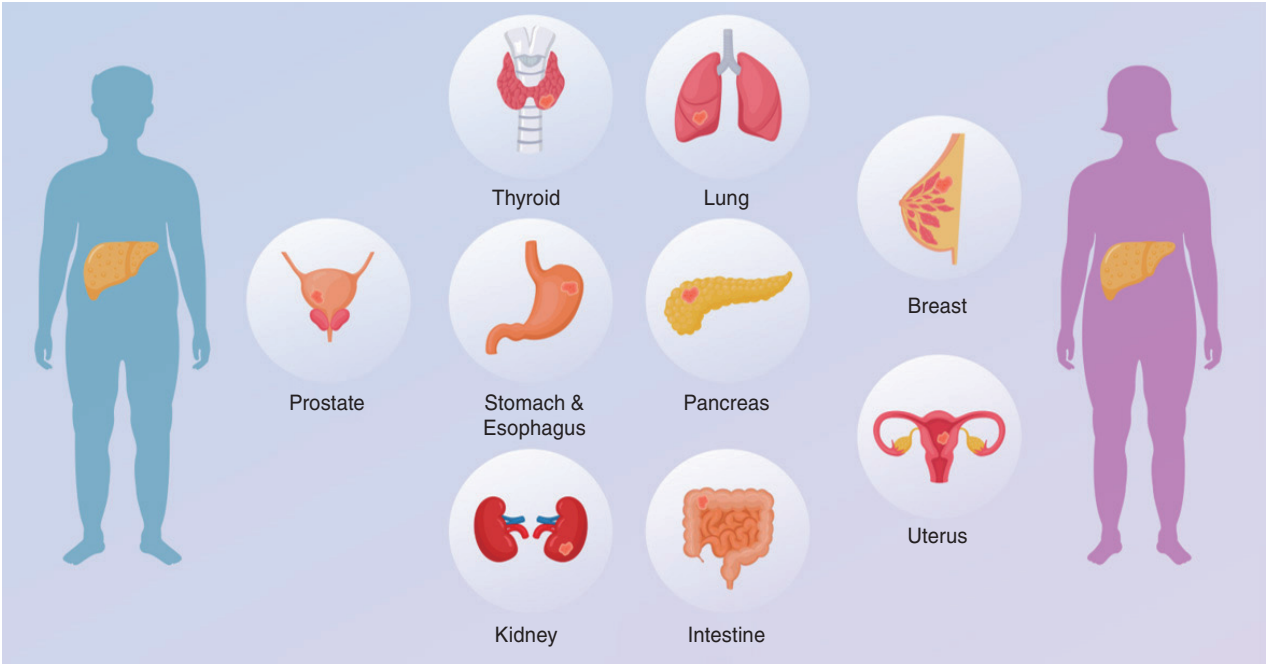

Figure 4. MASLD-related extrahepatic malignancies. MASLD, metabolic dysfunction-associated steatotic liver disease.

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stages per year and a cumulative progression rate of 42% over a follow-up period of 6.6 years.[86] In a meta-analysis of 11 cohort studies, including 411 biopsy-confirmed patients with NAFLD, the annual liver fibrosis progression rate was 0.13 stages. Progression by at least one stage was estimated to take 14.3 years for NAFL and 7.1 years for NASH, with fibrosis progression occurring approximately twice as fast in NASH compared to NAFL.[87] Moderate alcohol consumption has been identified as a factor influencing fibrosis progression in patients with NAFLD. A study of 58,927 patients with NAFLD in Korea reported that men and women consuming 10.0–29.9 or 10.0–19.9 g of alcohol per day, respectively, had a 1.29–1.31 times higher risk of fibrosis progression compared to non-drinkers (fibrosis-4 [FIB-4] index: 95% CI 1.18–1.40, NAFLD fibrosis score [NFS]: 1.23–1.40).[88] Furthermore, a meta-analysis of 32 cohort and cross-sectional studies found that moderate alcohol consumption increased the risk of progressive fibrosis by 1.39 times (95% CI 1.22–1.57) in cohort studies, although no significant association was observed in cross-sectional studies.[89]

Research on the prevalence and incidence of liver fibrosis and cirrhosis in MAFLD and MASLD remains scarce. A prospective study of 202 biopsy-confirmed patients with MAFLD reported the following prevalence of liver fibrosis stages: F1: 40.6%, F2: 6.9%, F3: 24.8%, and F4: 2.5%, with a 27.3% prevalence of advanced fibrosis (F3–4).[90] Moreover, a study of 969,253 patients with MAFLD without cirrhosis from the US Veterans Affairs Database, tracking patients from 2010 to 2020, reported 5-year and 10-year cirrhosis incidence rates of 2.42% (95% CI 2.39–2.45) and 3.70% (95% CI 3.66–3.74), respectively.[91] A recent Korean study investigated the epidemiology of SLD, which is defined as an FLI ≥30, in a cohort of 9,497 individuals from the Ansung–Ansan cohort, with biennial follow-ups from 2002 to 2020. The study found that 26.7% of individuals with MASLD had significant liver fibrosis, defined using age-adjusted FIB-4 criteria (FIB-4 ≥1.3 for individuals aged 35–64 years and FIB-4 ≥2.0 for those aged ≥65 years). After adjusting for factors influencing fibrosis, the risk of developing significant liver fibrosis was 1.39 times higher (95% CI 1.25–1.55) in the MASLD group compared to those without SLD.[46] Another Korean study conducted from January 2017 to May 2020, involving 7,918 health check-up participants who underwent magnetic resonance elastography (MRE), reported that the average liver stiffness measurement (LSM) in individuals with MASLD was 2.3 kPa, which was consistent with the overall average of all participants. The proportion of individuals with progressive liver fibrosis (MRE LSM ≥3.6 kPa) was found to be very low, at 2.4%.[41] The prevalence of liver fibrosis and progressive liver fibrosis varies across studies owing to differences in diagnostic methods and criteria. A study conducted between 2009 and 2010 involving 369,094 health check-up participants in Korea found that individuals with MASLD had a 1.71-fold increased risk (95% CI 1.58–1.85) of developing cirrhosis and 1.45-fold increased risk (95% CI 1.29–1.62) of developing decompensated cirrhosis compared to those without SLD. Additionally, in the MASLD population, alcohol consumption was associated with a significantly higher risk of cirrhosis and decompensated cirrhosis, with respective risks of 2.31 folds (95% CI 2.05–2.61) and 1.77 folds (95% CI 1.47–2.14) compared to the MASLD group without significant alcohol intake.[92] Recent studies have reported that moderate alcohol consumption (100–200 g/week for men and 100–130 g/week for women) in individuals with MASLD increases the risk of significant liver fibrosis (LSM ≥8 kPa) by 2.71 folds (95% CI 1.77–4.13).[93] Consequently, moderate or low levels of alcohol intake in individuals with MASLD could potentially influence liver fibrosis, highlighting the need for caution. However, further studies, including prospective research, are needed to provide more definitive evidence on this matter.

As outlined, the progression of liver fibrosis and the development of cirrhosis in patients with MASLD are significant determinants of disease severity and prognosis. Liver fibrosis is generally assessed using liver biopsy as the gold standard. However, noninvasive methods can be used when biopsy is not practical. For diagnosing liver fibrosis in patients with MASLD, transient elastography, shear wave elastography, and MRE are potential diagnostic tools, whereas serum markers can be used to exclude the presence of progressive liver fibrosis.[94] For detailed information on the methods and accuracy of individual noninvasive tests, refer to the '2024 Korean Society of Hepatology Clinical Practice Guidelines for Noninvasive Assessment of Liver Fibrosis in Chronic Liver Disease'.[94]

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[Summary]

- Liver fibrosis progression and the potential cirrhosis development in patients with MASLD are critical determinants of disease severity and prognosis. Noninvasive diagnostic tools for assessing liver fibrosis in these patients are guided by the '2024 Clinical Practice Guidelines for Noninvasive Evaluation of Liver Fibrosis in Chronic Liver Diseases' from the KASL.

Mortality

During a median follow-up of 14.2 years, the all-cause mortality in patients with biopsy-proven NAFLD (n=10,568) and matched controls (n=49,925) was 28.6 and 16.9/1,000 person-years, respectively. All-cause mortality was higher in patients with NAFLD than in matched controls (adjusted HR 1.93, 95% CI 1.86–2.00).[95] A meta-analysis revealed that the leading causes of death in NAFLD were cardiovascular disease, extrahepatic malignancy, and liver-related events. All-cause mortality from CVD, extrahepatic malignancy, and liver-related events in NAFLD were 5.54, 4.21, and 1.75/1,000 person-years, respectively.[96] Several cohort studies showed that liver fibrosis is closely associated with mortality in patients with NAFLD.[97,98] The critical factor for mortality is the stage of liver fibrosis in patients with NAFLD. Significant fibrosis (≥F2) is an independent factor for all-cause and liver-related mortality in NAFLD, which increases in the presence of significant fibrosis (≥F2).[99] Compared to controls, all-cause mortality increased in NAFL (HR 1.71, 95% CI 1.64–1.7), NASH without fibrosis (HR 2.14, 95% CI 1.93–2.38), non-cirrhotic fibrosis (HR 2.44, 95% CI 2.22–2.69), and cirrhosis (HR 3.79, 95% CI 3.34–4.30) in a large cohort study based on biopsy.[95] Therefore, all-cause and liver-related mortality were associated with the presence of steatohepatitis and fibrosis in patients with NAFLD.[95] T2DM is also a risk factor for mortality in patients with NAFLD. A US study using NHANES data showed that all-cause mortality was higher in patients with NAFLD and T2DM than in individuals without both of these (HR 1.35, 95% CI 1.19–1.52) or in those with NAFLD without T2DM (HR 1.60, 95% CI 1.38–1.85).[100] A Korean study using KNHANES data showed that the use of anti-diabetic drugs, including sodium-glucose cotransporter 2 (SGLT2) inhibitors, reduced liver-related events and mortality in 87,178 patients with NAFLD and T2DM.[101]

During a median follow-up of 22.83 years, there was no significant difference in all-cause mortality between NAFLD (n=2,736) and MASLD (n=2,600) in a US study using NHANES data. All-cause mortality in patients with NAFLD and MASLD was 20.19 and 21.109/1,000 person-years, respectively (P>0.05).[55] There was a similar tendency of all-cause mortality between NAFLD and MASLD, although patients with MASLD were slightly older and had a slightly increased CVD-related mortality.[55] Another US study using NHANES data investigated the all-cause mortality of 2,264 patients with MASLD with a median follow-up duration of 27.1 years. All-cause mortality in MASLD was higher in patients with advanced fibrosis than in those without it (HR 1.53, 95% CI 1.13–2.06).[102] A recent Korean study using KNHANES data also revealed that all-cause mortality is higher in patients with MASLD than in those without it (HR 1.32, 95% CI 1.18–1.48).[103] All-cause mortality increased in patients with MASLD with significant fibrosis (HR 1.68, 95% CI 1.42–2.00) and in those with T2DM (HR 1.85, 95% CI 1.55–2.21). MASLD with significant fibrosis and T2DM were at high risk of all-cause mortality (HR 2.29, 95% CI 1.77–2.98).[103] Liver transplantation was done in 31 patients (14%), and death occurred in 73 (33.1%) during a median follow-up of 3.2 years among 220 patients with MASLD-related decompensated cirrhosis.[72]

[Summary]

- All-cause and liver-related mortality increase in MASLD with steatohepatitis and advanced fibrosis.

Impact of cardiometabolic factors in MASLD

High BMI and central obesity are associated with poor prognosis in patients with MASLD. Compared to BMI 25–30 kg/m^2, severe obesity (≥50 kg/m^2) has a higher risk of hepatic decompensation, obesity-related extrahepatic cancers, and all-cause mortality.[104] The US NHANES III shows that all-cause mortality increase as waist circumference and waist-to-hip ratio increases in patients with MASLD.[105] T2DM is an independent risk factor for fibrosis progression in patients with MASLD. In 447 patients with biopsy-proven MASLD, fibrosis progression with ≥1-stage increase in participants with T2DM compared to participants without

T2DM (adjusted HR, 1.69, 95% CI 1.17–2.43).[106] A meta-analysis reveals that participants with T2DM had a significantly higher risk of hepatic decompensation and HCC development in MASLD.[107] Also, diabetes is a risk factor for all-cause mortality in patients with MASLD. A Korean study showed that all-cause mortality is higher in MASLD patients with diabetes than in those without it (HR 1.85, 95% CI 1.55–2.21).[103] A cohort study diagnosing MASLD using transient elastography showed that the severity of liver fibrosis worsened as the number of cardiometabolic risk factors increased.[93] A prospective cohort study in Korea, which followed 10,038 patients with MASLD for 17.5 years using a FLI ≥30, found that hypertension significantly increased the risk of cardiovascular disease (aHR 1.94, 95% CI 1.63–2.31). The same study reported that an increase in cardiometabolic risk factors was associated with a higher risk of cardiovascular disease.[46] A 9-year study using NHIS in Korea, where MASLD was defined using an FLI ≥30 found that MASLD with hypertension had the highest cardiovascular disease-related mortality compared to other cardiometabolic risk factors. Additionally, MASLD patients with low HDL exhibited the highest all-cause, liver-related, and cancer-related mortality.[108]

DRUG TREATMENTS FOR MASH

General principle of use

As the need for MASH treatment has increased, clinical studies on various drugs have been conducted to improve MASH and liver fibrosis. The complex pathophysiology of MASH and its interaction with other metabolic diseases remain poorly understood. As a result, the current therapeutic agents for MASH are under development, targeting a wide range of targets. Here, the mechanisms of their use are introduced and effects of previously introduced and newly developed drugs are discussed.

Antioxidants

Vitamin E, an antioxidant, improves intrahepatic inflammation by reducing oxidative stress that worsens NASH.[109,110] In the large-scale randomized phase III PIVENS study, high-dose vitamin E (800 IU/day) administration for 96 weeks showed significant improvement in intrahepatic inflammation as measured by histological examination compared to the control group (43% vs. 19%, *P*=0.001). However, no improvement in liver fibrosis was observed.[111] The resolution rate of NASH, a secondary endpoint, was 36% in vitamin E, which was higher than 21% in the control group. However, long-term administration of vitamin E increases the incidence of prostate cancer and hemorrhagic stroke; hence, caution is required for long-term use.[112] Furthermore, controversial, high-dose vitamin E (>400 IU/day) administration may be associated with increased mortality; thus, caution is advised regarding safety.[113-115] However, a retrospective study showed that in 236 patients with advanced liver fibrosis or cirrhosis due to histologically proven NASH, regardless of the presence of T2DM, the use of vitamin E (800 IU/day) for >2 years reduced the risk of death, liver transplantation, and decompensated cirrhosis, but no difference was observed in the incidence of HCC, vascular disease, or extrahepatic cancer.[116] Additional studies are needed to evaluate the histological efficacy of vitamin E on MASH and liver fibrosis.

Insulin resistance-improving drugs

Pioglitazone is a peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist that improves insulin resistance in adipose tissue, muscle, and liver, enhances mitochondrial function in hepatocytes to reduce hepatic fat, and improves hepatocyte damage.[117-120] According to four randomized controlled trials, histological steatohepatitis findings were improved in the pioglitazone-administered group (30 or 45 mg/day) regardless of the presence or absence of T2DM compared to the placebo group.[111,121-123] However, no improvement in liver fibrosis, a major indicator predicting the progression of liver disease, was observed.[111,121,122,124,125] In the PIVENS study, 247 patients with steatohepatitis without T2DM were divided into the pioglitazone (30 mg/day), vitamin E (800 IU/day), and control groups, with administration observed for 96 weeks.[111] The primary endpoint was a decrease of ≥2 points in the NAFLD Activity Score (NAS), defined as an improvement of at least 1 point in ballooning degeneration and a decrease of at least 1 point in fat accumulation or lobular inflammation. The study results showed that the pioglitazone group was more effective than the control group (19% in the control group and 34% in the pioglitazone group (*P*=0.04). However, as the PIVENS study

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compared three groups, statistical significance was determined only when the *P*-value was <0.025 in comparison between the two groups. It was, therefore, reported that the pioglitazone group did not affect liver histological findings. Although this drug has beneficial effects on insulin sensitivity, blood sugar control, serum lipids, and prevention of CVD in patients with T2DM,[126,127] it may have adverse effects such as weight gain, leg edema, hemodilution due to fluid accumulation, post-menopausal bone loss, and risk of bladder cancer.[128] However, to date, there have been no large-scale international phase III clinical trials on pioglitazone for the improvement of steatohepatitis and liver fibrosis. Therefore, in the future, it is necessary to confirm the histological efficacy of pioglitazone on steatohepatitis and liver fibrosis in patients with MASH without cirrhosis through a large-scale phase III clinical trial.

Other drugs

CVD is the most common cause of death in NAFLD; therefore, correcting the CVD risk factors is crucial.[81,129,130] Since increased plasma lipoprotein increases carotid intima-media thickness and atherosclerotic plaques, which contribute to CVD, preventing and treating dyslipidemia is necessary.[131] Lipid-lowering agents such as statins (hydroxy-methyl-glutaryl coenzyme A reductase inhibitors) can be used in patients with NAFLD and dyslipidemia.[132-134] As only <1% of patients discontinued statin treatment owing to hepatotoxicity, statins safely lowered liver enzyme levels and reduced the incidence of CVD in patients with NAFLD and elevated liver enzyme levels.[135] In a domestic study using data from the National Health Insurance Service, statin administration lowered the incidence of NAFLD regardless of the presence of T2DM. It also reduced the progression of liver fibrosis after NAFLD onset.[136] If low-density lipoprotein cholesterol (LDL-C) is not strictly controlled after statin administration, the incidence of CVD increases; therefore, thorough control is necessary.[137] A common side effect of statins is asymptomatic elevation of liver enzyme levels, which mostly occurs within 1 year of starting treatment and usually recovers spontaneously.[138] This elevation of liver enzyme levels is proportional to the statin dose.[139] However, there was no difference in the occurrence of persistent and significant elevations or adverse effects of liver and biliary tract diseases compared to the control group;[140] hence, statin administration is possible in chronic liver diseases, including NAFLD.[141,142] However, statin administration should be avoided in decompensated cirrhosis and acute liver failure.[143-146] Case-control studies have shown that statins are associated with a reduced risk of steatosis, steatohepatitis, and liver fibrosis,[147] as well as a reduced risk of decompensated risk, mortality, and HCC in patients with cirrhosis.[148] Previous studies were conducted on patients with NAFLD; however, considering that there was no significant difference in the study group when applied to patients with MASLD,[55] it is recommended that statins be used in MASLD and be considered as a primary treatment to lower LDL-C to prevent atherosclerotic CVD. However, to date, no large-scale randomized controlled trials have shown that statin drugs directly improve the histology of MASLD.

Omega-3 polyunsaturated fatty acids (eicosapentaenoic acid) showed a decrease in intrahepatic fat mass in MRI compared to placebo in clinical trials conducted on patients with NASH. However, they did not show improvement in NASH or liver fibrosis in liver biopsy.[149,150] Metformin did not show improvement in steatohepatitis or liver fibrosis in patients with NASH when administered alone in a randomized controlled clinical trial.[151] However, in a retrospective observational study, the use of metformin in patients with NAFLD with T2DM and advanced fibrosis or cirrhosis prolonged the period until liver transplantation. It decreased the risk of HCC and extrahepatic carcinoma.[152] In addition, there have been reports that hepatotonics such as ursodeoxycholic acid, silymarin, S-adenosyl-L methionine, and dimethyl-4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxybiphenyl-2,2′-dicarboxylate can improve fatigue, hepatic fat, liver enzyme levels, and metabolic indices.[153,154] Therefore, these hepatotonics may be considered on case-by-case basis as an adjunct. However, further research is needed on the histological improvement effect in patients with MASH.

Current status of new drugs for MASH that are being newly introduced

Recently, no clinical study has been conducted directly on this disease since the term MASLD was newly introduced. All previous studies were related to NASH in patients with NAFLD. However, despite the term NAFLD being changed to MASLD, it is known that the group of patients with NAFLD and that with MASLD are mostly the same.[55] Therefore, it is judged that there will be no signifi-

cant issue in using NASH-related treatment drugs as MASH treatments.

Selective THR-β agonist

Recently, on March 14, 2024, the US Food and Drug Administration (US FDA) approved resmetirom for the first time as a drug treatment for NASH.[155] This drug was developed to target a selective THR-β agonist. It selectively acts on intrahepatic THR-β to induce conversion of T4 to T3 in the liver, improves damaged mitochondrial function, lowers intrahepatic lipid accumulation, and induces improvement of intrahepatic inflammation and liver fibrosis. (Fig. 5) A phase III clinical trial was conducted on patients with NASH with F2/F3 liver fibrosis without cirrhosis.[156,157]

The relative liver-specific expression of selective THR-β agonists lowers blood cholesterol and triglyceride levels, increases intrahepatic bile acid synthesis, and plays an important role in intrahepatic fatty acid oxidation.[158,159] In a multicenter, randomized, double-blind, placebo-controlled study (MAESTRO-NASH) involving 1,759 patients with NASH with histologically diagnosed F2/F3 liver fibrosis, resmetirom, a selective THR-β agonist, showed significant improvement in steatohepatitis in 25.9% of the 80-mg group and 29.9% of the 100-mg group without worsening of liver fibrosis compared to placebo (9.7%) (P<0.001).[157] Improvement in liver fibrosis of one or more stages was observed in 24% of the 80-mg group and 26% of the 100-mg group, which was statistically significant compared to 14% of the placebo group (P<0.001). Compared with baseline, at 24 weeks after treatment, the reduction in LDL-C levels was 13.6% in the 80-mg group and 16.3% in the 100-mg group, compared with 0.1% in the placebo group (P<0.001).[157] The most common adverse effects were diarrhea and nausea, which occurred more frequently in the resmetirom group than in the placebo group. However, the incidence of serious adverse events was similar across the study groups (10.9% in the 80-mg group, 12.7% in the 100-mg group, and 11.5% in the placebo group). It. is important to take the patient's medical history and to monitor any of these adverse effects each time they visit the hospital. In conclusion, resmetirom demonstrated histologic improvement in steatohepatitis and fibrosis in adult patients with NASH without cirrhosis and F2/F3 fibrosis in a large phase III study, with its safety profile being similar to that of the placebo group. Therefore, resmetirom can be administered

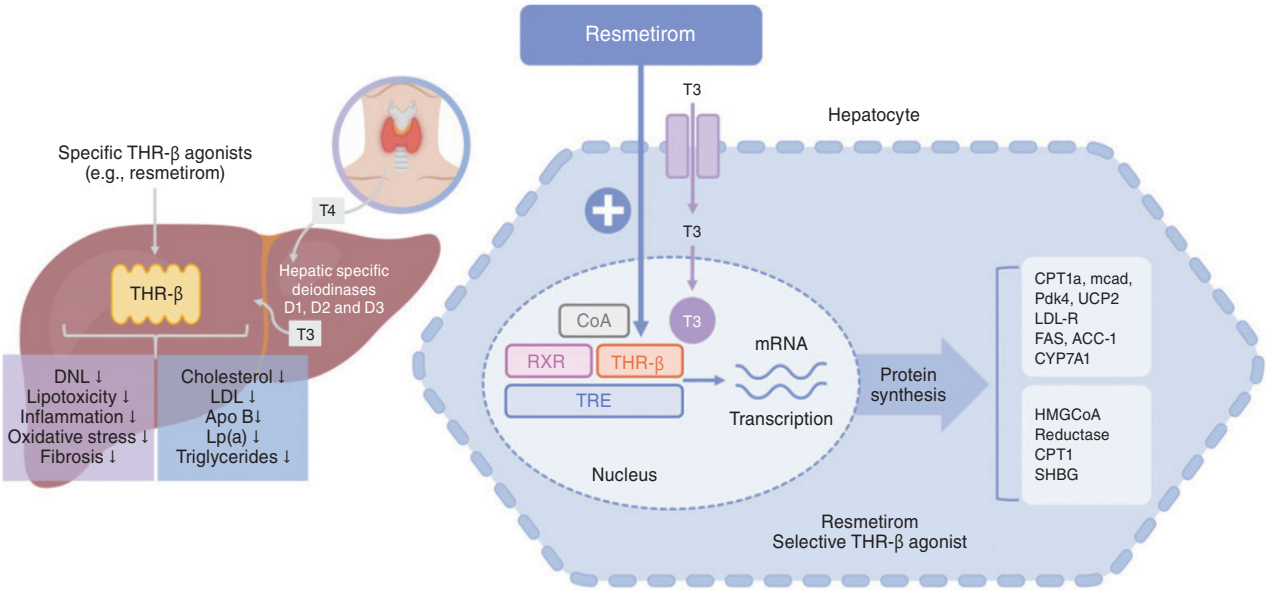

Figure 5. Intrahepatic mechanism of action of selective thyroid hormone receptor-β agonists. THR, thyroid hormone receptor; T4, thyroxine; T3, tri-iodothyronine; DNL, de novo lipogenesis; LDL, low-density lipoprotein; Apo B, apolipoprotein B; Lp(a), low lipoprotein(a); CoA, coenzyme A; RXR, retinoid X receptor; THR, thyroid hormone receptor; TRE, tetracyclin-responsive element; CPT1a, carnitine palmitoyltransferase 1; mcad, medium-chain acyl-coenzyme A dehydrogenase; Pdk4, pyruvate dehydrogenase kinase 4; UCP2, uncoupling protein 2; LDL-R; low-density lipoprotein receptor; FAS, fatty acid synthase; ACC-1, acetyl coenzyme A carboxylase; CYP7A1, cholesterol 7 alpha-hydroxylase; HMG-CoA, 3-hydroxyl-3-methyl-glutaryl-coenzyme A; SHBG, sex hormone binding globulin.

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in these conditions.

However, there is a lack of data on the efficacy and safety of long-term resmetirom use. The approved drug (resmetirom) may not be readily available to the general public due to its currently estimated high cost, especially in Asia. The number of patients who responded was only 20–30% of the entire treatment group. In addition, most of the enrolled patients belonged to the Western population, and considering the different characteristics between Western and Asian population, further validation of existing research results in a larger Asian population would be more helpful for the generalizability of drug (resmetirom) use. In addition, there remain issues such as whether to discontinue the drug and when to discontinue it. Therefore, although with FDA's accelerated approval, resmetirom can be used, attention should be paid to the long-term follow-up results on its use up to 54 months, which will be reported in the future.

Other drugs undergoing phase III clinical trials

Phase III clinical trials are in progress on drugs targeting various mechanisms, such as glucagon-like peptide-1 (GLP-1) receptor agonist (semaglutide), pan-PPAR agonist (lanifibranor), fibroblast growth factor 21 (FGF21) agonist (pegozafermin and efruxifermin), glucagon/GLP-1 receptor agonist (survodutide), and fatty acid synthase (FASN) inhibitor (denifanstat) (Table 3). The phase III clinical trial of SGLT2 inhibitor (dapagliflozin) ended in March 2024, and the results are expected to be announced soon. In the case of dapagliflozin, the results of the phase III clinical trial for NASH have not been announced yet; therefore, it is difficult to use it immediately to improve steatohepatitis and liver fibrosis. However, it can be used for the treatment of each accompanying disease in patients with dyslipidemia accompanied by T2DM, heart failure, and chronic renal failure. The phase III clinical study of semaglutide for metabolic dyslipidemia completed patient enrollment in August 2024. However, the clinical results have not yet been announced; therefore, it is difficult to use it currently to improve steatohepatitis and liver fibrosis. However, if the final results of the phase III clinical study confirm positive therapeutic effect on steatohepatitis, it can be used to improve obesity and T2DM as well as steatohepatitis and liver fibrosis in patients with metabolic dyslipidemia. Studies of lanifibranor, pegozafermin, efruxifermin, survodutide, and denifanstat are currently enrolling patients, and the results of these studies are expected. Another clinical study is related to the drug aramchol, a stearoyl-CoA desaturase 1 (SCD 1) inhibitor. The open-label Part I study achieved its study objectives, but the double-blind Part II study has now been suspended.[160,161] In addition, obeticholic acid, a farnesoid X receptor (FXR) agonist, was studied in patients with NASH with F1-3 fibrosis. However, the FDA rejected its approval owing to safety issues related to hepatotoxicity and skin itching.[162,163] The drugs in phase III clinical trials are summarized in Table 3.

[Recommendation]

- Resmetirom can be used as a therapeutic agent in patients with MASH with F2/F3 liver fibrosis as histological improvement of steatohepatitis and liver fibrosis has been proven. (A1)
- Vitamin E can be expected to improve steatohepatitis in patients with MASH without T2DM, and pioglitazone can be expected to improve steatohepatitis in patients with MASH regardless of T2DM. However, their effects on improving liver fibrosis are not clear. (B2)
- Statins can be used to prevent CVD in patients with MASH accompanied by dyslipidemia. GLP-1 receptor agonists can be used to treat obesity and T2DM in patients with MASH. SGLT2 inhibitors can be used to improve concomitant diseases in patients with MASH accompanied by T2DM, heart failure, and chronic renal failure. (B1)

PEDIATRIC PATIENTS

Nomenclature of SLD in children and adolescents

The term 'NAFLD' has been in use for decades in pediatrics. However, the term 'nonalcoholic' has been controversial in pediatrics because it might be misleading about fatty liver in children and adolescents. Inborn errors of metabolism cause fatty liver in children. It did not exactly differentiate fatty liver from alcohol use disorder in adolescents. Pa-

Table 3. Drugs for treating MASH in phase III clinical trials (as of December 18, 2024)

Drug	Mechanism	NCT number	Subjects	Actual study start sate	Estimated study completion date	Current status
Resmetirom	Selective THR-β agonist	MAESTRO-NASH (NCT03900429)	NASH, fibrosis (F2 or 3)	March 28, 2019	January 2028	FDA approval (March 14, 2024), active, not recruiting
Semaglutide	GLP-1 RA	ESSENCE (NCT04822181)	NASH, fibrosis (F2 or 3)	April 1, 2021	April 25, 2029	active, not recruiting
Dapagliflozin	SGLT2 inhibitor	DEAN (NCT03723252)	NASH	March 20, 2019	March 28, 2024	Completed
Lanifibranor	Pan-PPAR agonist	NATIV3 (NCT04849728)	NASH, fibrosis (F2 or 3)	August 19, 2021	September 30, 2026	Ongoing, recruiting
Aramchol	SCD1 inhibitor	ARMOR (NCT04104321)	NASH, fibrosis (F2 or 3)	September 23, 2019	June 2027	Double blind part: suspended
Pegozafermin	FGF21 agonist	ENLIGHTEN-Fibrosis (NCT06318169)	NASH, fibrosis (F2 or 3)	March 13, 2024	February 2029	Ongoing, recruiting
Efruxifermin	Homodimeric human IgG1 Fc-FGF21 fusion protein	SYNCHRONY (1) Real-World (NCT06161571), (2) Histology (NCT06215716), (3) Outcomes (NCT06528314)	(1) noninvasively diagnosed MAFLD or MASH (2) MASH fibrosis (F2-3) (3) MASH Fibrosis (F4)	(1) Nov 10, 2023 (2) Dec 1, 2023 (3) June 10, 2024	(1) Oct, 2026 (2) March, 2027 (3) Oct, 2029	Ongoing, recruiting
Survodutide	Glucagon/GLP-1 RA	LIVERAGE (NCT06632444)	MASH, fibrosis (F2 or 3)	Oct 14, 2024	Dec 27, 2031	Ongoing, recruiting
Denifanstat	FASN inhibitor	(1) FASCINATE-3(NCT06594523) (2) FASCINIT (NCT06692283)	(1) MASH fibrosis (F2-3) (2) MASLD/MASH	(1) Dec 1, 2024 (2) Jan 1, 2025	(1) Dec, 2030 (2) June, 2027	Not yet recruiting

MASH, metabolic dysfunction-associated steatohepatitis; NASH, nonalcoholic steatohepatitis; THR, thyroid hormone receptor; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2; PPAR, peroxisome proliferator-activated receptor; SCD-1; stearoyl-CoA desaturase 1; FGF21, fibroblast growth factor 21; FASN, fatty acid synthase; FDA, food and drug administration; Oct, October; Nov, November; Dec, December; Jan, January; NCT, national clinical trial.

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tients with NAFLD tend to be unmotivated to modify their lifestyles actively because the term 'fatty' was felt to be stigmatizing to the Western population.[164] Some have suggested that the term 'NAFLD' does not reflect metabolic dysfunction, which is the disease characteristic. In this context, 'MAFLD' was suggested considering metabolic dysfunction in FLD in adults[14] and children[165] in 2020. However, MAFLD also includes the term 'fatty', and it does not differentiate other causes of the development of hepatic steatosis from metabolic dysfunction.

A multisociety Delphi consensus statement on new FLD nomenclature was released in 2023. The term 'SLD' was adopted as a comprehensive concept on intrahepatic fat accumulation.[18] Instead of NAFLD, MASLD was suggested as a new concept of fatty liver, considering metabolic dysfunctions such as obesity, insulin resistance, and T2DM. The diagnostic criteria of MASLD are intrahepatic fat accumulation in the presence of at least one of the cardiometabolic risk factors in adults.[166] The same cardiometabolic risk factors are applied to children and adolescents for defining the diagnostic criteria of MASLD.[18]

Diagnosis of MASLD in pediatrics

NAFLD is exclusive of other causes for intrahepatic fat accumulation.[167,168] The diagnostic criteria of MASLD was the presence of hepatic steatosis with at least one of the cardiometabolic risk factors in pediatrics (Table 4).[18] Hepatic steatosis in MASLD is defined based on an imaging study or liver biopsy.

Perspective on MASLD in pediatrics

A multi-society of pediatric gastroenterology in Europe, North America, Latin America, and Asia endorsed 'MASLD' as a new nomenclature in January 2024.[169] The diagnosis

Table 4. Diagnostic criteria of cardiometabolic factors in MASLD in children and adolescents

Pediatric criteria - at least 1 out of 5
BMI ≥85th percentile for age/sex [BMI z-score ≥ +1] or WC > 95th percentile or ethnicity adjusted equivalent
Fasting serum glucose ≥100 mg/dL (5.6 mmol/L) or serum glucose ≥200 mg/dL (11.1 mmol/L) or 2-hour postprandial glucose levels ≥140 mg/dL (7.8 mmol/L) or HbA1c ≥5.7% (39 mmol/L) or already diagnosed/treated type 2 diabetes or treatment for type 2 diabetes
Blood pressure: age <13 years, BP ≥95th percentile or ≥130/80 mmHg (whichever is lower); age ≥13 years, 130/85 mmHg or specific antihypertensive drug treatment
Plasma triglycerides: age <10 years, ≥100 mg/dL (1.15 mmol/L); age ≥10 years, ≥150 mg/dL (1.70 mmol/L) or lipid lowering treatment
Plasma HDL-cholesterol ≤40 mg/dL (1.0 mmol/L) or lipid lowering treatment

MASLD, metabolic dysfunction-associated steatotic liver disease; BMI, body mass index; WC, waist circumference; BP, blood pressure; HDL, high-density lipoprotein.

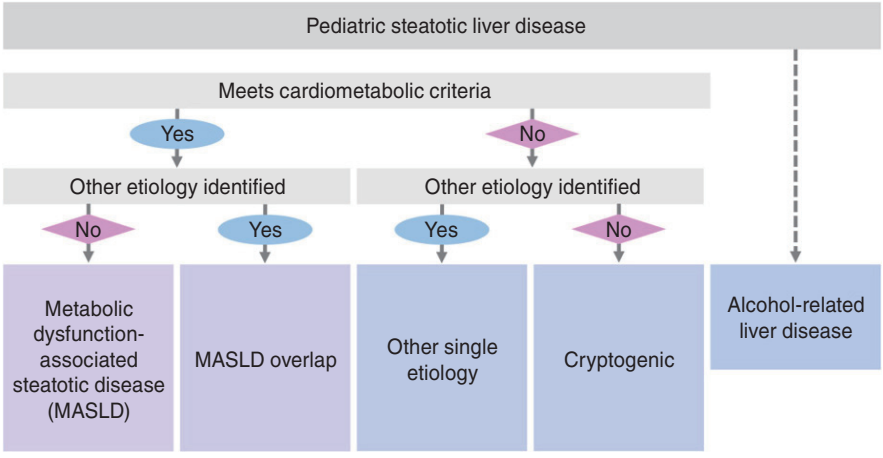

Figure 6. Steatotic liver disease and subgroup in pediatrics.

of SLD in pediatrics is based on the pathophysiological mechanism of hepatic steatosis in children and adolescents (Fig. 6). However, there is a possibility that the diagnosis of MASLD overlap is underestimated because of Wilson's disease, autoimmune hepatitis, and inborn errors of metabolism on hepatic steatosis.[170] MASLD is closely associated with insulin resistance, T2DM, and dyslipidemia.[171,172]

The prevalence of MASLD overlap in pediatrics will increase as the prevalence of overweight or obesity increases.[173] In pediatrics, 'metabolic liver disease' is an inborn error of metabolism such as urea cycle disorder, organic acidemia, aminoaciduria, lysosome disorder, and fatty acid oxidation disorder. However, the term 'metabolic' in MASLD means metabolic syndrome related to insulin resistance rather than an inborn error of metabolism. Therefore, if SLD is atypical (with no cardiometabolic risk factor) in pediatrics, an inborn error of metabolism or inherited single gene defects causing metabolic disease are suspected.[169]

Epidemiology of MASLD in pediatrics

A meta-analysis of 62 studies showed that the prevalence of NAFLD in pediatrics and adolescents was 13% and 46% in the general population and obese individuals, respectively.[174] A Korean study using data from KNHANES indicated that the prevalence of NAFLD in Korean pediatric patients and adolescents increased from 8.2% in 2009 to 12.1% in 2018.[175]

There is a lack of epidemiologic studies on MASLD in pediatric patients and adolescents. A normal range of serum ALT is observed in 20% of biopsy-proven NAFLD in pediatrics.[176] This suggests that the prevalence of MASLD in pediatric patients may be underestimated in the general population compared to the diagnosis of NAFLD considering serum ALT levels.[177]

Among 1410 adolescents (12–19 years) in the NHANES, the prevalence of SLD, defined as ≥240 dB/m in TE, was 30.5%. Approximately 85% of adolescents with NAFLD met the criteria for MASLD in the study.[178] Compared to NAFLD, MASLD had an advantage in screening high-risk cardiometabolic disease. There were high levels of HOMA-IR uric acid and triglyceride/H0|-cholesterol ratio in MASLD compared to NAFLD.[179]

Consideration in the diagnosis of MASLD in pediatrics

If MASLD is suspected in pediatrics, various etiologies for chronic liver disease should be considered. Autoimmune disease, Wilson's disease, viral hepatitis, alcohol use disorder, and drug-induced liver injury would be checked regardless of the presence of cardiometabolic risk factors.[169] These considerations depend on clinical situations. Early investigation for the diseases mentioned above should be considered if SLD in pediatrics possesses the 'red flags,' which are young age (<8 years), BMI z-score <1, neurodevelopmental delay, significant splenomegaly, synthetic dysfunction, or a history suggestive of an alternative diagnosis.[180] Additionally, other causes for SLD can be investigated if hepatic steatosis does not improve after weight reduction is performed in children and adolescents with obesity.[169] Alcohol-related liver disease is uncommon as a primary etiology of SLD in pediatrics. Further studies are needed to clarify several issues on MASLD in pediatric patients and adolescents as follows: (1) the concordance rate between NAFLD and MASLD in the same cohort of pediatric patients and adolescents; (2) large-scale studies for epidemiology and natural course of pediatric MASLD; and (3) impact of other causes for SLD on MASLD overlap in pediatrics.[169]

[Summary]

- MASLD in pediatrics is defined as the presence of hepatic steatosis on imaging studies or liver biopsy and the presence of at least one cardiometabolic risk factor.
- Various etiologies except cardiometabolic factors for hepatic steatosis is considered in the diagnosis of MASLD in pediatrics.

Authors' contributions

List of author contributions is available at the official website of Clinical and Molecular Hepatology (Supplementary Table 1, https://doi.org/10.3350/cmh.2025.0045).

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Conflicts of Interest

Conflicts of interest statement is available at the official website of Clinical and Molecular Hepatology (Supplementary Table 3, https://doi.org/10.3350/cmh.2025.0045).

SUPPLEMENTAL MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (http://www.e-cmh.org).

REFERENCES

1. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-394.
2. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-406.
3. Schünemann H, Brożek J, Guyatt G, Oxman A. GRADE Handbook. <https://gdt.gradepro.org/app/handbook/handbook.html>. Accessed 11 Dec 2024.
4. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719-725.
5. Addison T. Observations on fatty degeneration of the liver. Guys Hosp Rep 1836;1:485.
6. Budd G. On diseases of the liver. 3rd ed. London: John Churchill, 1857.
7. Pepper W. Saccharine diabetes. Med Rec 1884;25:9-12.
8. Brunt EM, Neuschwander-Tetri BA, Burt AD. Fatty liver disease: Alcoholic and nonalcoholic. In: Burt AD, Portmann B, Ferrell L, ed. MacSween's Pathology of the Liver. 6th ed. Elsevier, 2011:293-359.
9. Adler M, Schaffner F. Fatty liver hepatitis and cirrhosis in obese patients. Am J Med 1979;67:811-816.
10. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc 1980;55:434-438.
11. Lee RG. Nonalcoholic steatohepatitis: a study of 49 patients. Hum Pathol 1989;20:594-598.
12. Schaffner F, Thaler H. Nonalcoholic fatty liver disease. Prog Liver Dis. 1986;8:283-98.
13. Eslam M, Sanyal AJ, George J. Toward more accurate nomenclature for fatty liver diseases. Gastroenterology 2019;157:590-593.
14. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73:202-209.
15. Ratziu V, Rinella M, Beuers U, Loomba R, Anstee QM, Harrison S, et al. The times they are a-changin' (for NAFLD as well). J Hepatol 2020;73:1307-1309.
16. Younossi ZM, Rinella ME, Sanyal AJ, Harrison SA, Brunt EM, Goodman Z, et al. From NAFLD to MAFLD: Implications of a premature change in terminology. Hepatology 2021;73:1194-1198.
17. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology 2023;78:1966-1986.
18. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79:1542-1556.
19. Nonalcoholic Fatty Liver Disease (NAFLD) Nomenclature Revision Consensus Task Force on behalf of the Korean Association for the Study of the Liver (KASL). A new Korean nomenclature for steatotic liver disease. Clin Mol Hepatol 2024;30(Suppl):S214-S216.
20. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-1402.
21. Kang SH, Lee HW, Yoo JJ, Cho Y, Kim SU, Lee TH, et al. KASL clinical practice guidelines: Management of nonalcoholic fatty liver disease. Clin Mol Hepatol 2021;27:363-401.
22. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158:1999-2014.e1.
23. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A consensus statement from the international diabetes federation. Diabet Med 2006;23:469-480.
24. Haam JH, Kim BT, Kim EM, Kwon H, Kang JH, Park JH, et

al. Diagnosis of obesity: 2022 Update of clinical practice guidelines for obesity by the Korean Society for the Study of Obesity. J Obes Metab Syndr 2023;32:121-129.
25. Kim HJ, Kang DR, Kim JY, Kim W, Jeong YW, Chun KH, et al. Metabolic syndrome fact sheet 2024: Executive report. Cardiometab Syndr J 2024;4:70-80.
26. World Health Organization. Regional Office for the Western Pacific. The Asia-Pacific perspective: redefining obesity and its treatment. Sydney: Health Communications Australia. 2000. <https://iris.who.int/handle/10665/206936>. Accessed 11 Dec 2024.
27. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33.
28. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42:503-508.
29. Ratziu V, Boursier J; AFEF Group for the Study of Liver Fibrosis. Confirmatory biomarker diagnostic studies are not needed when transitioning from NAFLD to MASLD. J Hepatol 2024;80:e51-e52.
30. Hagström H, Vessby J, Ekstedt M, Shang Y. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical. J Hepatol 2024;80:e76-e77.
31. Lee BP, Dodge JL, Terrault NA. National prevalence estimates for steatotic liver disease and subclassifications using consensus nomenclature. Hepatology 2024;79:666-673.
32. Lee CM, Yoon EL, Kim M, Kang BK, Cho S, Nah EH, et al. Prevalence, distribution, and hepatic fibrosis burden of the different subtypes of steatotic liver disease in primary care settings. Hepatology 2024;79:1393-1400.
33. Jeong EH, Jun DW, Cho YK, Choe YG, Ryu S, Lee SM, et al. Regional prevalence of non-alcoholic fatty liver disease in Seoul and Gyeonggi-do, Korea. Clin Mol Hepatol 2013;19:266-272.
34. Im HJ, Ahn YC, Wang JH, Lee MM, Son CG. Systematic review on the prevalence of nonalcoholic fatty liver disease in South Korea. Clin Res Hepatol Gastroenterol 2021;45:101526.
35. Li J, Zou B, Yeo YH, Feng Y, Xie X, Lee DH, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2019;4:389-398.
36. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2022;7:851-861.
37. Lee HW, Kim BK, Kim SU, Park JY, Kim DY, Ahn SH, et al. Prevalence and predictors of significant fibrosis among subjects with transient elastography-defined nonalcoholic fatty liver disease. Dig Dis Sci 2017;62:2150-2158.
38. Lee JY, Kim KM, Lee SG, Yu E, Lim YS, Lee HC, et al. Prevalence and risk factors of non-alcoholic fatty liver disease in potential living liver donors in Korea: a review of 589 consecutive liver biopsies in a single center. J Hepatol 2007;47:239-244.
39. Kim M, Yoon EL, Cho S, Lee CM, Kang BK, Park H, et al. Prevalence of advanced hepatic fibrosis and comorbidity in metabolic dysfunction-associated fatty liver disease in Korea. Liver Int 2022;42:1536-1544.
40. Lee H, Lee YH, Kim SU, Kim HC. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: A nationwide cohort study. Clin Gastroenterol Hepatol 2021;19:2138-2147.e10.
41. Oh JH, Ahn SB, Cho S, Nah EH, Yoon EL, Jun DW. Diagnostic performance of non-invasive tests in patients with MetALD in a health check-up cohort. J Hepatol 2024;81:772-780.
42. Park HJ, Lee S, Lee JS. Differences in the prevalence of NAFLD, MAFLD, and MASLD according to changes in the nomenclature in a health check-up using MRI-derived proton density fat fraction. Abdom Radiol (NY) 2024;49:3036-3044.
43. Lee HH, Lee HA, Kim EJ, Kim HY, Kim HC, Ahn SH, et al. Metabolic dysfunction-associated steatotic liver disease and risk of cardiovascular disease. Gut 2024;73:533-540.
44. Joo SK, Kim W. Sex differences in metabolic dysfunction-associated steatotic liver disease: a narrative review. Ewha Med J 2024;47:e17
45. Moon JH, Jeong S, Jang H, Koo BK, Kim W. Metabolic dysfunction-associated steatotic liver disease increases the risk of incident cardiovascular disease: a nationwide cohort study. EClinicalMedicine 2023;65:102292.
46. Choe HJ, Moon JH, Kim W, Koo BK, Cho NH. Steatotic liver disease predicts cardiovascular disease and advanced liver fibrosis: A community-dwelling cohort study with 20-year follow-up. Metabolism 2024;153:155800.
47. Chang Y, Ryu S, Sung E, Jang Y. Higher concentrations of alanine aminotransferase within the reference interval predict nonalcoholic fatty liver disease. Clin Chem 2007;53:686-692.
48. Chang Y, Jung HS, Cho J, Zhang Y, Yun KE, Lazo M, et al. Metabolically healthy obesity and the development of nonal-

https://doi.org/10.3350/cmh.2025.0045

coholic fatty liver disease. Am J Gastroenterol 2016;111:1133-1140.
49. Lee MJ, Kim EH, Bae SJ, Kim GA, Park SW, Choe J, et al. Age-related decrease in skeletal muscle mass is an independent risk factor for incident nonalcoholic fatty liver disease: A 10-year retrospective cohort study. Gut Liver 2019;13:67-76.
50. Kim D, Chung GE, Kwak MS, Seo HB, Kang JH, Kim W, et al. Body fat distribution and risk of incident and regressed nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2016;14:132-138.e4.
51. Jung HS, Chang Y, Kwon MJ, Sung E, Yun KE, Cho YK, et al. Smoking and the risk of non-alcoholic fatty liver disease: A cohort study. Am J Gastroenterol 2019;114:453-463.
52. Kim D, Chung GE, Kwak MS, Kim YJ, Yoon JH. Effect of longitudinal changes of body fat on the incidence and regression of nonalcoholic fatty liver disease. Dig Liver Dis 2018;50:389-395.
53. Kim TJ, Sinn DH, Min YW, Son HJ, Kim JJ, Chang Y, et al. A cohort study on Helicobacter pylori infection associated with nonalcoholic fatty liver disease. J Gastroenterol 2017;52:1201-1210.
54. Sinn DH, Cho SJ, Gu S, Seong D, Kang D, Kim H, et al. Persistent nonalcoholic fatty liver disease increases risk for carotid atherosclerosis. Gastroenterology 2016;151:481-488.e1.
55. Younossi ZM, Paik JM, Stepanova M, Ong J, Alqahtani S, Henry L. Clinical profiles and mortality rates are similar for metabolic dysfunction-associated steatotic liver disease and non-alcoholic fatty liver disease. J Hepatol 2024;80:694-701.
56. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024;81:492-542.
57. Simon TG, Roelstraete B, Hagström H, Sundström J, Ludvigsson JF. Non-alcoholic fatty liver disease and incident major adverse cardiovascular events: results from a nationwide histology cohort. Gut 2022;71:1867-1875.
58. Kim D, Konyn P, Sandhu KK, Dennis BB, Cheung AC, Ahmed A. Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. J Hepatol 2021;75:1284-1291.
59. Le MH, Le DM, Baez TC, Dang H, Nguyen VH, Lee K, et al. Global incidence of adverse clinical events in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Clin Mol Hepatol 2024;30:235-246.
60. Mantovani A, Csermely A, Petracca G, Beatrice G, Corey KE, Simon TG, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2021;6:903-913.
61. Zhao Q, Deng Y. Comparison of mortality outcomes in individuals with MASLD and/or MAFLD. J Hepatol 2024;80:e62-e64.
62. Treeprasertsuk S, Leverage S, Adams LA, Lindor KD, St Sauver J, Angulo P. The Framingham risk score and heart disease in nonalcoholic fatty liver disease. Liver Int 2012;32:945-950.
63. Golabi P, Fukui N, Paik J, Sayiner M, Mishra A, Younossi ZM. Mortality risk detected by atherosclerotic cardiovascular disease score in patients with nonalcoholic fatty liver disease. Hepatol Commun 2019;3:1050-1060.
64. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021;42:3227-3337.
65. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-249.
66. Kanwal F, Kramer JR, Mapakshi S, Natarajan Y, Chayanupatkul M, Richardson PA, et al. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. Gastroenterology 2018;155:1828-1837.e2.
67. Song BG, Choi SC, Goh MJ, Kang W, Sinn DH, Gwak GY, et al. Metabolic dysfunction-associated fatty liver disease and the risk of hepatocellular carcinoma. JHEP Rep 2023;5:100810.
68. Yun B, Park H, Ahn SH, Oh J, Kim BK, Yoon JH. Liver cancer risk across metabolic dysfunction-associated steatotic liver disease and/or alcohol: A nationwide study. Am J Gastroenterol 2025;120:410-419.
69. Jeong S, Oh YH, Ahn JC, Choi S, Park SJ, Kim HJ, et al. Evolutionary changes in metabolic dysfunction-associated steatotic liver disease and risk of hepatocellular carcinoma: A nationwide cohort study. Clin Mol Hepatol 2024;30:487-499.
70. Song BG, Kim A, Goh MJ, Kang W, Gwak GY, Paik YH, et al. Risk of hepatocellular carcinoma by steatotic liver disease and its newly proposed subclassification. Liver Cancer 2024;13:

561-571.
71. Chen YT, Chen TI, Yang TH, Yin SC, Lu SN, Liu XR, et al. Long-term risks of cirrhosis and hepatocellular carcinoma across steatotic liver disease subtypes. Am J Gastroenterol 2024;119:2241-2250.
72. Noureddin N, Huang DQ, Bettencourt R, Siddiqi H, Majzoub AM, Nayfeh T, et al. Natural history of clinical outcomes and hepatic decompensation in metabolic dysfunction-associated steatotic liver disease. Aliment Pharmacol Ther 2024;59:1521-1526.
73. Mantovani A, Petracca G, Beatrice G, Csermely A, Tilg H, Byrne CD, et al. Non-alcoholic fatty liver disease and increased risk of incident extrahepatic cancers: a meta-analysis of observational cohort studies. Gut 2022;71:778-788.
74. Yi M, Peng W, Feng X, Teng F, Tang Y, Kong Q, et al. Extrahepatic morbidities and mortality of NAFLD: an umbrella review of meta-analyses. Aliment Pharmacol Ther 2022;56:1119-1130.
75. Kim GA, Lee HC, Choe J, Kim MJ, Lee MJ, Chang HS, et al. Association between non-alcoholic fatty liver disease and cancer incidence rate. J Hepatol 2018;68:140-146.
76. Thomas JA, Kendall BJ, Dalais C, Macdonald GA, Thrift AP. Hepatocellular and extrahepatic cancers in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Eur J Cancer 2022;173:250-262.
77. Chung GE, Yu SJ, Yoo JJ, Cho Y, Lee KN, Shin DW, et al. Differential risk of 23 site-specific incident cancers and cancer-related mortality among patients with metabolic dysfunction-associated fatty liver disease: a population-based cohort study with 9.7 million Korean subjects. Cancer Commun (Lond) 2023;43:863-876.
78. Yuan X, Wang X, Wu S, Chen S, Wang Y, Wang J, et al. Associations between metabolic dysfunction-associated fatty liver disease and extrahepatic cancers: a cohort in China. Hepatobiliary Surg Nutr 2023;12:671-681.
79. Liu Z, Lin C, Suo C, Zhao R, Jin L, Zhang T, et al. Metabolic dysfunction-associated fatty liver disease and the risk of 24 specific cancers. Metabolism 2022;127:154955.
80. Powell EE, Roche S, Sarraf B, Hartel G, Skoien R, Leggett B, et al. Australians with metabolic dysfunction-associated steatotic liver disease have a twofold increase in the incidence of cancer. JGH Open 2024;8:e70000.
81. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-357.
82. Quek J, Chan KE, Wong ZY, Tan C, Tan B, Lim WH, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2023;8:20-30.
83. Ye Q, Zou B, Yeo YH, Li J, Huang DQ, Wu Y, et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:739-752.
84. Wong VW, Wong GL, Choi PC, Chan AW, Li MK, Chan HY, et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut 2010;59:969-974.
85. Pais R, Charlotte F, Fedchuk L, Bedossa P, Lebray P, Poynard T, et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatol 2013;59:550-556.
86. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015;62:1148-1155.
87. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13:643-654.e1-9; quiz e39-40.
88. Chang Y, Cho YK, Kim Y, Sung E, Ahn J, Jung HS, et al. Nonheavy drinking and worsening of noninvasive fibrosis markers in nonalcoholic fatty liver disease: A cohort study. Hepatology 2019;69:64-75.
89. Magherman L, Van Parys R, Pauwels NS, Verhelst X, Devisscher L, Van Vlierberghe H, et al. Meta-analysis: The impact of light-to-moderate alcohol consumption on progressive non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2023;57:820-836.
90. Chan WL, Chong SE, Chang F, Lai LL, Chuah KH, Nik Mustapha NR, et al. Long-term clinical outcomes of adults with metabolic dysfunction-associated fatty liver disease: a single-centre prospective cohort study with baseline liver biopsy. Hepatol Int 2023;17:870-881.
91. Yeoh A, Yang Z, Cheung R, Do A, Ahmed A, Wong RJ. Incidence of cirrhosis and hepatocellular carcinoma among

https://doi.org/10.3350/cmh.2025.0045

veterans with noncirrhotic metabolic dysfunction-associated fatty liver disease. J Clin Gastroenterol 2024;58:718-725.
92. Kim GA, Jeong S, Jang H, Lee DH, Joo SK, Kim W. Metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatotic liver disease with increased alcohol intake increase the risk of developing hepatocellular carcinoma and incident or decompensated cirrhosis: A Korean nationwide study. Liver Cancer 2023;13:426-437.
93. Marti-Aguado D, Calleja JL, Vilar-Gomez E, Iruzubieta P, Rodríguez-Duque JC, Del Barrio M, et al. Low-to-moderate alcohol consumption is associated with increased fibrosis in individuals with metabolic dysfunction-associated steatotic liver disease. J Hepatol 2024;81:930-940.
94. Kim MN, Han JW, An J, Kim BK, Jin YJ, Kim SS, et al. KASL clinical practice guidelines for noninvasive tests to assess liver fibrosis in chronic liver disease. Clin Mol Hepatol 2024;30(Suppl):S5-S105.
95. Simon TG, Roelstraete B, Khalili H, Hagström H, Ludvigsson JF. Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a nationwide cohort. Gut 2021;70:1375-1382.
96. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 2023;77:1335-1347.
97. Younossi ZM, Mangla KK, Berentzen TL, Grau K, Kjær MS, Ladelund S, et al. Liver histology is associated with long-term clinical outcomes in patients with metabolic dysfunction-associated steatohepatitis. Hepatol Commun 2024;8:e0423.
98. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389-397.e10.
99. Ng CH, Lim WH, Hui Lim GE, Hao Tan DJ, Syn N, Muthiah MD, et al. Mortality outcomes by fibrosis stage in nonalcoholic fatty liver disease: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2023;21:931-939.e5.
100. Ng CH, Chan KE, Chin YH, Zeng RW, Tsai PC, Lim WH, et al. The effect of diabetes and prediabetes on the prevalence, complications and mortality in nonalcoholic fatty liver disease. Clin Mol Hepatol 2022;28:565-574.
101. Jang H, Kim Y, Lee DH, Joo SK, Koo BK, Lim S, et al. Outcomes of various classes of oral antidiabetic drugs on nonalcoholic fatty liver disease. JAMA Intern Med 2024;184:375-383.
102. Kim D, Wijarnpreecha K, Cholankeril G, Ahmed A. Steatotic liver disease-associated all-cause/cause-specific mortality in the United States. Aliment Pharmacol Ther 2024;60:33-42.
103. Han E, Lee BW, Kang ES, Cha BS, Ahn SH, Lee YH, et al. Mortality in metabolic dysfunction-associated steatotic liver disease: A nationwide population-based cohort study. Metabolism 2024;152:155789.
104. Behari J, Wang R, Luu HN, McKenzie D, Molinari M, Yuan JM. Severe obesity is associated with worse outcomes than lean metabolic dysfunction-associated steatotic liver disease. Hepatol Commun 2024;8:e0471.
105. Chen J, Zhou H, Liu K. Normal weight and central obesity as predictors of increased all-cause mortality in metabolic dysfunction associated steatotic liver disease. J Hepatol 2024;80:e143-e145.
106. Ajmera V, Cepin S, Tesfai K, Hofflich H, Cadman K, Lopez S, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. J Hepatol 2023;78:471-478.
107. Huang DQ, Noureddin N, Ajmera V, Amangurbanova M, Bettencourt R, Truong E, et al. Type 2 diabetes, hepatic decompensation, and hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: an individual participant-level data meta-analysis. Lancet Gastroenterol Hepatol 2023;8:829-836.
108. Oh R, Kim S, Cho SH, Kim J, Lee YB, Jin SM, et al. Metabolic dysfunction-associated steatotic liver disease and all-cause and cause-specific mortality. Diabetes Metab J 2025;49:80-91.
109. Hasegawa T, Yoneda M, Nakamura K, Makino I, Terano A. Plasma transforming growth factor-beta1 level and efficacy of alpha-tocopherol in patients with non-alcoholic steatohepatitis: a pilot study. Aliment Pharmacol Ther 2001;15:1667-1672.
110. Harrison SA, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. Am J Gastroenterol 2003;98:2485-2490.
111. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362:1675-1685.
112. Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial

(SELECT). JAMA 2011;306:1549-1556.
113. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142:37-46.
114. Curtis AJ, Bullen M, Piccenna L, McNeil JJ. Vitamin E supplementation and mortality in healthy people: a meta-analysis of randomised controlled trials. Cardiovasc Drugs Ther 2014; 28:563-573.
115. Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, et al. Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: a systematic review and dose-response meta-analysis of prospective studies. Am J Clin Nutr 2018;108:1069-1091.
116. Vilar-Gomez E, Vuppalanchi R, Gawrieh S, Ghabril M, Saxena R, Cummings OW, et al. Vitamin E improves transplant-free survival and hepatic decompensation among patients with nonalcoholic steatohepatitis and advanced fibrosis. Hepatology 2020;71:495-509.
117. Marra F, Efsen E, Romanelli RG, Caligiuri A, Pastacaldi S, Batignani G, et al. Ligands of peroxisome proliferator-activated receptor gamma modulate profibrogenic and proinflammatory actions in hepatic stellate cells. Gastroenterology 2000; 119:466-478.
118. Galli A, Crabb DW, Ceni E, Salzano R, Mello T, Svegliati-Baroni G, et al. Antidiabetic thiazolidinediones inhibit collagen synthesis and hepatic stellate cell activation in vivo and in vitro. Gastroenterology 2002;122:1924-1940.
119. Bril F, Kalavalapalli S, Clark VC, Lomonaco R, Soldevila-Pico C, Liu IC, et al. Response to pioglitazone in patients with nonalcoholic steatohepatitis with vs without type 2 diabetes. Clin Gastroenterol Hepatol 2018;16:558-566.e2.
120. Kalavalapalli S, Bril F, Koelmel JP, Abdo K, Guingab J, Andrews P, et al. Pioglitazone improves hepatic mitochondrial function in a mouse model of nonalcoholic steatohepatitis. Am J Physiol Endocrinol Metab 2018;315:E163-E173.
121. Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology 2008;135:1176-1184.
122. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355: 2297-2307.
123. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: A randomized trial. Ann Intern Med 2016;165:305-315.
124. Ratziu V, Giral P, Jacqueminet S, Charlotte F, Hartemann-Heurtier A, Serfaty L, et al. Rosiglitazone for nonalcoholic steatohepatitis: one-year results of the randomized placebo-controlled Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) Trial. Gastroenterology 2008;135:100-110.
125. Ratziu V, Charlotte F, Bernhardt C, Giral P, Halbron M, Lenaour G, et al. Long-term efficacy of rosiglitazone in nonalcoholic steatohepatitis: results of the fatty liver improvement by rosiglitazone therapy (FLIRT 2) extension trial. Hepatology 2010; 51:445-453.
126. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279-1289.
127. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after Ischemic stroke or transient ischemic attack. N Engl J Med 2016;374:1321-1331.
128. Staels B, Butruille L, Francque S. Treating NASH by targeting peroxisome proliferator-activated receptors. J Hepatol 2023; 79:1302-1316.
129. Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 2015;61:1547-1554.
130. Tabenkin H, Eaton CB, Roberts MB, Parker DR, McMurray JH, Borkan J. Differences in cardiovascular disease risk factor management in primary care by sex of physician and patient. Ann Fam Med 2010;8:25-32.
131. Fracanzani AL, Burdick L, Raselli S, Pedotti P, Grigore L, Santorelli G, et al. Carotid artery intima-media thickness in nonalcoholic fatty liver disease. Am J Med 2008;121:72-78.
132. Rubinstein A. National Cholesterol Education Program, second report of the Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. Circulation 1995; 91:908-909
133. Pastori D, Polimeni L, Baratta F, Pani A, Del Ben M, Angelico F. The efficacy and safety of statins for the treatment of nonalcoholic fatty liver disease. Dig Liver Dis 2015;47:4-11.

https://doi.org/10.3350/cmh.2025.0045

134. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A Report of the American College of Cardiology/American heart association task force on clinical practice guidelines. J Am Coll Cardiol 2019;74: e177-e232.
135. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet 2010;376:1916-1922.
136. Lee JI, Lee HW, Lee KS, Lee HS, Park JY. Effects of statin use on the development and progression of nonalcoholic fatty liver disease: A nationwide nested case-control study. Am J Gastroenterol 2021;116:116-124.
137. Khoo S, Wong VW, Goh GB, Fan J, Chan WK, Seto WK, et al. Suboptimal treatment of dyslipidemia in patients with nonalcoholic fatty liver disease. J Gastroenterol Hepatol 2020;35: 320-325.
138. Chalasani N. Statins and hepatotoxicity: focus on patients with fatty liver. Hepatology 2005;41:690-695.
139. Dale KM, White CM, Henyan NN, Kluger J, Coleman CI. Impact of statin dosing intensity on transaminase and creatine kinase. Am J Med 2007;120:706-712.
140. Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol 2006;97:52C-60C.
141. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology 2004;126:1287-1292.
142. Lewis JH, Mortensen ME, Zweig S, Fusco MJ, Medoff JR, Belder R, et al. Efficacy and safety of high-dose pravastatin in hypercholesterolemic patients with well-compensated chronic liver disease: Results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial. Hepatology 2007; 46:1453-1463.
143. Bays H, Cohen DE, Chalasani N, Harrison SA, The national lipid association's statin safety task force. an assessment by the statin liver safety task force: 2014 update. J Clin Lipidol 2014;8(3 Suppl):S47-57.
144. Kumar S, Grace ND, Qamar AA. Statin use in patients with cirrhosis: a retrospective cohort study. Dig Dis Sci 2014;59: 1958-1965.
145. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(25 Suppl 2):S1-45.
146. Watanabe S, Hashimoto E, Ikejima K, Uto H, Ono M, Sumida Y, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. J Gastroenterol 2015;50:364-377.
147. Ayada I, van Kleef LA, Zhang H, Liu K, Li P, Abozaid YJ, et al. Dissecting the multifaceted impact of statin use on fatty liver disease: a multidimensional study. EBioMedicine 2023; 87:104392.
148. El-Serag HB, Johnson ML, Hachem C, Morgana RO. Statins are associated with a reduced risk of hepatocellular carcinoma in a large cohort of patients with diabetes. Gastroenterology 2009;136:1601-1608.
149. Sanyal AJ, Abdelmalek MF, Suzuki A, Cummings OW, Chojkier M; EPE-A Study Group. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. Gastroenterology 2014;147: 377-384.e1.
150. Argo CK, Patrie JT, Lackner C, Henry TD, de Lange EE, Weltman AL, et al. Effects of n-3 fish oil on metabolic and histological parameters in NASH: a double-blind, randomized, placebo-controlled trial. J Hepatol 2015;62:190-197.
151. Loomba R, Lutchman G, Kleiner DE, Ricks M, Feld JJ, Borg BB, et al. Clinical trial: pilot study of metformin for the treatment of non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2009;29:172-182.
152. Vilar-Gomez E, Vuppalanchi R, Desai AP, Gawrieh S, Ghabril M, Saxena R, et al. Long-term metformin use may improve clinical outcomes in diabetic patients with non-alcoholic steatohepatitis and bridging fibrosis or compensated cirrhosis. Aliment Pharmacol Ther 2019;50:317-328.
153. Baden KER, McClain H, Craig E, Gibson N, Draime JA, Chen AMH. S-Adenosylmethionine (SAMe) for liver health: A systematic review. Nutrients 2024;16:3668.
154. Lee HA, Chang Y, Sung PS, Yoon EL, Lee HW, Yoo JJ, et al. Therapeutic mechanisms and beneficial effects of non-antidiabetic drugs in chronic liver diseases. Clin Mol Hepatol 2022; 28:425-472.
155. U.S. Food and Drug Administration. FDA approves first treatment for patients with liver scarring due to fatty liver disease. FDA web site, <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-liver-

scarring-due-fatty-liver-disease>. Accessed 11 Dec 2024.
156. Harrison SA, Taub R, Neff GW, Lucas KJ, Labriola D, Moussa SE, et al. Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. Nat Med 2023;29:2919-2928.
157. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al. A Phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med 2024;390: 497-509.
158. Reinehr T. Obesity and thyroid function. Mol Cell Endocrinol 2010;316:165-171.
159. Sinha RA, Bruinstroop E, Singh BK, Yen PM. Nonalcoholic fatty liver disease and hypercholesterolemia: Roles of thyroid hormones, metabolites, and agonists. Thyroid 2019;29:1173-1191.
160. Ratziu V, de Guevara L, Safadi R, Poordad F, Fuster F, Flores-Figueroa J, et al. Aramchol in patients with nonalcoholic steatohepatitis: a randomized, double-blind, placebo-controlled phase 2b trial. Nat Med 2021;27:1825-1835.
161. National Institutes of Health (NIH). A Clinical Study to Evaluate the efficacy and safety of aramchol in subjects with NASH (ARMOR). NIH web site, <https://clinicaltrials.gov/study/NCT04104321>. Accessed 11 Dec 2024.
162. Younossi ZM, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, et al. Obeticholic acid for the treatment of nonalcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019;394:2184-2196.
163. Ratziu V. Obeticholic acid for the treatment of nonalcoholic steatohepatitis. Clin Liver Dis (Hoboken) 2021;17:398-400.
164. Lazarus JV, Kakalou C, Palayew A, Karamanidou C, Maramis C, Natsiavas P, et al. A Twitter discourse analysis of negative feelings and stigma related to NAFLD, NASH and obesity. Liver Int 2021;41:2295-2307.
165. Eslam M, Alkhouri N, Vajro P, Baumann U, Weiss R, Socha P, et al. Defining paediatric metabolic (dysfunction)-associated fatty liver disease: an international expert consensus statement. Lancet Gastroenterol Hepatol 2021;6:864-873.
166. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-1645.
167. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: Recommendations from the expert committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr 2017;64:319-334.
168. Vajro P, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. J Pediatr Gastroenterol Nutr 2012;54: 700-713.
169. European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN); European Association for the Study of the Liver (EASL); North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN); Latin-American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (LASPGHAN); Asian Pan-Pacific Society for Pediatric Gastroenterology, Hepatology and Nutrition (APPSPGHAN); Pan Arab Society for Pediatric Gastroenterology and Nutrition (PASPGHAN), et al. Paediatric steatotic liver disease has unique characteristics: A multisociety statement endorsing the new nomenclature. J Pediatr Gastroenterol Nutr 2024;78:1190-1196.
170. European Society for Paediatric Gastroenterology Hepatology (ESPGHAN) and European Association for the Study of the Liver (EASL), on behalf of co-authors. Diagnosis of fatty liver in children should occur in parallel to investigation for other causes of liver disease. Lancet Gastroenterol Hepatol 2023;8: 598-600.
171. Perry RJ, Samuel VT, Petersen KF, Shulman GI. The role of hepatic lipids in hepatic insulin resistance and type 2 diabetes. Nature 2014;510:84-91.
172. Smith GI, Shankaran M, Yoshino M, Schweitzer GG, Chondronikola M, Beals JW, et al. Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease. J Clin Invest 2020;130:1453-1460.
173. Schwimmer JB, Newton KP, Awai HI, Choi LJ, Garcia MA, Ellis LL, et al. Paediatric gastroenterology evaluation of overweight and obese children referred from primary care for suspected non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2013;38:1267-1277.
174. Lee EJ, Choi M, Ahn SB, Yoo JJ, Kang SH, Cho Y, et al. Prevalence of nonalcoholic fatty liver disease in pediatrics and

https://doi.org/10.3350/cmh.2025.0045

adolescents: a systematic review and meta-analysis. World J Pediatr 2024;20:569-580.
175. Song K, Park G, Lee HS, Lee M, Lee HI, Ahn J, et al. Trends in prediabetes and non-alcoholic fatty liver disease associated with abdominal obesity among Korean children and adolescents: Based on the Korea national health and nutrition examination survey between 2009 and 2018. Biomedicines 2022; 10:584.
176. Draijer LG, van Oosterhout JPM, Vali Y, Zwetsloot S, van der Lee JH, van Etten-Jamaludin FS, et al. Diagnostic accuracy of fibrosis tests in children with non-alcoholic fatty liver disease: A systematic review. Liver Int 2021;41:2087-2100.
177. Mouzaki M, Speakman A, Xanthakos S. Goodbye, NAFLD, hello, MASLD?! J Pediatr Gastroenterol Nutr 2024;79:198-201.
178. Ma N, Bansal M, Chu J, Branch AD. Fibrosis and steatotic liver disease in US adolescents according to the new nomenclature. J Pediatr Gastroenterol Nutr 2024;79:229-237.
179. Di Sessa A, Guarino S, Umano GR, Miraglia Del Giudice E, Marzuillo P. Uric acid in pediatric MASLD definition: Is it time to implement diagnostic criteria? J Hepatol 2024;80:e254-e255.
180. Hegarty R, Deheragoda M, Fitzpatrick E, Dhawan A. Paediatric fatty liver disease (PeFLD): All is not NAFLD - Pathophysiological insights and approach to management. J Hepatol 2018; 68:1286-1299.