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An Expert Consensus Delphi Panel in Metabolic Dysfunction- and Alcohol-associated Liver Disease: Opportunities and Challenges in Clinical Practice

Luis Antonio Diaz,[1,2] Veeral Ajmera,[1] Juan Pablo Arab,[2,3] Daniel Q. Huang,[4,5] Cynthia Hsu,[1] Brian P. Lee,[6,7] Alexandre Louvet,[8,9] Maja Thiele,[10,11] Federica Tavaglione,[1] Monica Tincopa,[1] Elisa Pose,[12] Leon A. Adams,[13] William Alazawi,[14] Marco Arrese,[2] Ramon Bataller,[12] Ajay Duseja,[15] Suthat Liangpunsakul,[16] Michael R. Lucey,[17] Philippe Mathurin,[8,9] Jessica Mellinger,[18] Atsushi Nakajima,[19] Vlad Ratziu,[20,21,22,23] Nancy Reau,[24] Mary E. Rinella,[25] Mark Thursz,[26] Vincent Wai-Sun Wong,[27] Patrick S. Kamath,[28] and Rohit Loomba[1]

[1]MASLD Research Center, Division of Gastroenterology and Hepatology, University of California San Diego, San Diego, California; [2]Departamento de Gastroenterología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; [3]Division of Gastroenterology, Hepatology, and Nutrition, Department of Internal Medicine, Virginia Commonwealth University School of Medicine, Richmond, Virginia; [4]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; [5]Division of Gastroenterology and Hepatology, Department of Medicine, National University Health System, Singapore, Singapore; [6]Division of Gastroenterology and Liver Diseases, University of Southern California Keck School of Medicine, Los Angeles, California; [7]Institute for Addiction Science, University of Southern California, Los Angeles, California; [8]Service des Maladies de l'Appareil Digestif, University Hospital of Lille, Lille, France; [9]Unité INSERM Infinite, Lille, France; [10]Center for Liver Research, Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark; [11]Institute of Clinical Research, University of Southern Denmark, Odense, Denmark; [12]Liver Unit, Hospital Clinic and Institut d'Investigacions Biomediques August Pi I Sunyer (IDIBAPS), Barcelona, Spain; [13]Medical School, University of Western Australia, Perth, WA, Australia; [14]Barts Liver Centre, Blizard Institute, Queen Mary University London, London, United Kingdom; [15]Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; [16]Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, and Roudebush Veterans Administration Medical Center, Indianapolis, Indiana; [17]Department of Medicine, Division of Gastroenterology and Hepatology, University of Wisconsin, Madison, Wisconsin; [18]Henry Ford Health-Michigan State University, Detroit, Michigan; [19]Department of Gastroenterology and Hepatology, Graduate School of Medicine, Yokohama City University, Yokohama, Japan; [20]Sorbonne Université, Paris, France; [21]ICAN (Institute of Cardiometabolism and Nutrition), Paris, France; [22]Assistance Publique-Hôpitaux De Paris, Hôpital Pitié-Salpêtrière, Paris, France; [23]INSERM UMRS 1138 CRC, Paris, France; [24]Section of Hepatology, Hepatology Services, Rush University Medical Center, Chicago, Illinois; [25]University of Chicago, Pritzker School of Medicine, Chicago, Illinois; [26]Department of Metabolism, Digestion & Reproduction, Imperial College London, United Kingdom; [27]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China; and [28]Division of Gastroenterology and Hepatology, Mayo Clinic College of Medicine and Science, Rochester, Minnesota

BACKGROUND & AIMS: **Metabolic dysfunction- and alcohol-associated liver disease (MetALD) is a recently defined entity for individuals with liver steatosis, metabolic dysfunction, and increased alcohol intake. However, the current definition of MetALD poses multiple challenges in clinical practice and research. In this Delphi consensus, we provide practical recommendations for the clinical assessment and management of MetALD to address current clinical challenges in MetALD.**

Abbreviations used in this paper: **AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; AUDIT-C, Alcohol Use Disorders Identification Test Concise; BMI, body mass index; EASL, European Association for the Study of the Liver; FIB-4, Fibrosis-4; HbA1c, glycated hemoglobin; HCC, hepatocellular carcinoma; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; IQR, interquartile range; MASLD, metabolic dysfunction-associated steatotic liver disease; MBOAT7, membrane bound O-acyltransferase domain containing 7; MetALD, metabolic dysfunction- and alcohol-associated liver disease; NIAAA, National Institute on Alcohol Abuse and Alcoholism; NIT, non-invasive test; PEth, phosphatidylethanol; PNPLA3, patatin-like phospholipase domain 3; R1, first round; R2, second round; RR, response rate; SD, standard deviation; SLD, steatotic liver disease; TLFB, timeline follow-back; TM6SF2, transmembrane 6 superfamily member 2; UNOS, United Network for Organ Sharing; WHO, World Health Organization.**

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METHODS: We used a modified Delphi process, including 2 surveys involving a panel of 28 experts from 10 countries spanning 4 continents. We predefined consensus as requiring an ≥80% agreement.

RESULTS: The panel reached consensus on 28 statements. Recommendations emphasize the importance of a comprehensive assessment of patients with presumed MetALD, including the quantification of alcohol intake using validated questionnaires and the use of objective biomarkers of alcohol use, such as phosphatidylethanol. The need to reassess metabolic risk factors and liver disease after a period of alcohol abstinence was highlighted to distinguish the primary driver of liver injury. Noninvasive tests were recommended to assess liver disease severity, whereas routine liver biopsy was deemed unnecessary unless other diagnoses were suspected. Comprehensive management strategies should involve multidisciplinary care focusing on lifestyle modifications, alcohol reduction or cessation, weight loss, and exercise. Finally, the panel identified significant gaps in knowledge, advocating for standardized research protocols, longitudinal studies, exploration of pathophysiological mechanisms to inform precision medicine approaches, and the validation of quantitative alcohol biomarkers for identifying MetALD.

CONCLUSIONS: This Delphi consensus provides clear recommendations for the clinical assessment and management of MetALD, addressing the unique challenges posed by this condition.

Keywords: Alcohol-related Liver Disease; MASLD; Metabolic Dysfunction-associated Steatotic Liver Disease; NAFLD; Non-alcoholic Fatty Liver Disease.

Steatotic liver disease (SLD) is a major contributor to the global burden of liver disease worldwide.[1] In 2023, new criteria for SLD introduced a distinct entity—metabolic dysfunction and alcohol-associated liver disease (MetALD)—to describe patients with a dual liver injury due to both metabolic dysfunction and increased alcohol intake.[2] Thus, MetALD applies to individuals with liver steatosis, metabolic dysfunction, and self-reported alcohol consumption within the narrow range of 140 to 350 grams/week for females and 210 to 420 grams/week for males.[3] Although significant progress has been made in understanding how metabolic factors and alcohol intake together influence the onset and progression of SLD, their combined impact on the disease's natural history remains inadequately characterized.[4,5] Concerns and difficulties in clinical practice led to a collaborative effort from hepatologists, gastroenterologists, and endocrinologists to discuss key aspects of clinical assessment and comprehensive management strategies for individuals with MetALD using a structured Delphi consensus. This manuscript summarizes the Delphi process and the results of the consensus to provide recommendations for clinicians in the assessment and treatment of individuals with MetALD.

Methods

Panel Generation and Development of the Statements

The panel for this Delphi study comprised clinicians directly involved in the care of patients with MetALD and leading researchers in the SLD field. The steering committee was composed of 9 members actively involved in clinical and/or qualitative research (Veeral Ajmera, Juan Pablo Arab, Luis Antonio Díaz, Cynthia Hsu, Daniel Huang, Brian Lee, Rohit Loomba, Alexandre Louvet, and Maja Thiele), and 19 other members were invited based on their expertise in the field, prioritizing diversity in the topics to be discussed (expertise in metabolic dysfunction-associated steatotic liver disease [MASLD], MetALD, or alcohol-associated liver disease [ALD]) and geographic representation.

A modified Delphi method was used to reach consensus, incorporating insights from the literature and a diverse panel of content experts.[3,6] A PubMed/MEDLINE search was conducted to identify relevant literature on MetALD and related conditions, using search terms such as "MetALD" OR "steatotic liver disease" OR "fatty liver" OR "non-alcoholic fatty liver disease" OR "alcohol-related liver disease." Studies published through July 31, 2024, were reviewed by the steering committee to develop the areas and statements to discuss. Because limited evidence exists on MetALD, a narrative review was performed rather than a formal systematic review. The steering committee identified 5 domains deemed fundamental for discussion: (1) clinical assessment of patients with suspected MetALD; (2) natural history and progression of MetALD; (3) biomarkers for MetALD; (4) comprehensive management strategies for MetALD; and (5) considerations for clinical trials and gaps of knowledge in MetALD. A total of 27 statements across these domains were offered for the Delphi process (Figure 1 and Supplementary Table 1).

Delphi Rounds and Data Collection

A total of 28 clinical practice experts were invited to participate in the Delphi panel (Figure 1). The characteristics of Delphi panel participants, including

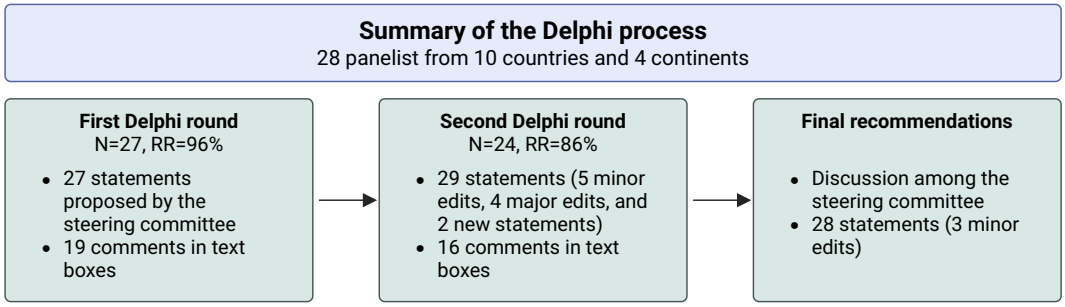

Figure 1. Summary of the Delphi process to provide recommendations in the clinical management of MetALD. This summary includes changes in statements and response rate obtained for each round.

demographics, professional expertise, and geographic representation, are summarized in Table 1. Consensus was defined a priori as a rate of $\geq$ 80% to ensure strong agreement before acceptance.[7] The Delphi process was conducted in 2 rounds using online data collection via the Qualtrics platform. The first-round (R1) survey was administered from August 30 to September 19, 2024, followed by the second-round (R2) survey from September 23 to October 28, 2024. Draft consensus statements utilized 5-point Likert-type response options, ranging from "strongly disagree" to "strongly agree." Panelists could also provide additional comments and suggest edits for each statement in accompanying text boxes. These comments were reviewed by the steering committee and used to refine statements for R2.

Table 1. Main Sociodemographic Characteristics of Panelists Included in the Delphi Consensus

Professional characteristics	Data
Sex	
Male	20 (71)
Female	8 (29)
Primary sector of employment	
Academic	26 (93)
Public	2 (7)
Other	0 (0)
Primary area of work	
Clinical research	21 (75)
Health care provider	6 (21)
Non-clinical research	1 (4)
Primary area of expertise	
Hepatology	26 (92)
Endocrinology	1 (4)
Psychiatry	1 (4)
Years working in the field post-training[a]	18.5 (7–25)
Number of articles (co)authored on topic of SLD	
<20	4 (14)
21–50	8 (29)
>51	16 (57)

Note: Data are presented as number (%) or median (interquartile range).
SLD, steatotic liver disease.

Statistical Analysis

Nominal data were described using percentages. In both Delphi rounds, data were assessed using the median and interquartile range (IQR) and a group median of 4 to 5 was considered to indicate agreement ($\geq$80% on a scale from 1 to 5). The stability of results was assessed using a Wilcoxon matched-pairs signed-rank test.[8] This test can be used to assess whether there is a significant change in responses between rounds, indicating whether stability has been achieved. To maximize validity, standard deviation (SD) was recorded to demonstrate convergence of results. A *P*-value $\leq$ .05 was considered significant. All analyses were performed with STATA software version 18 (StataCorp).

Results

Delphi Panel Characteristics and Responses

We included 28 panelists from 10 countries and 4 continents (Figure 1). Eight panelists (29%) were female, and the main areas of expertise were hepatology in 26 (92%), endocrinology in 1 (4%), and psychiatry in 1 (4%). The median years of experience post-training was 18.5 years (IQR, 7–25 years) (Table 1). Twenty-six of the panelists (93%) were from the academic sector, and 2 (7%) were from the public sector. The main fields/areas of work were clinical research in 21 (75%), followed by clinical care in 6 (21%), and non-clinical research in 1 (4%). Research productivity background was also considerable, with 8 participants (29%) having authored between 20 and 50 publications, and 16 (57%) having authored more than 50 publications on the topic of SLD (Table 1).

The R1 survey consisted of 27 statements within the five domains. A total of 27 out of 28 panelists participated and rated these statements (response rate [RR] of 96%). They also provided 19 comments that were reviewed and incorporated in the survey (Supplementary Table 1). Based on this feedback, the steering committee modified the statements for the R2 survey, comprising 29 statements that included 5 with minor edits, 4 with major edits, and 2 new statements.

Twenty-four panelists participated in the R2 (RR of 86%), providing 16 additional comments in a final open-ended text box (Supplementary Table 2). After the R2, all statements fulfilled agreement criteria, and 93% evidenced stability between R1 and R2 (Supplementary Table 2).

Recommendations from the Panel

The final recommendations that emerged from the Delphi consensus are available in Table 2 and Box 1. In the following sections, we provide an in-depth explanation of the recommendations and the current supporting data.

Clinical Assessment of Patients with Steatotic Liver Disease

Recommendations 1 to 10. Patients with SLD can present with heterogeneous manifestations across the disease spectrum.[9] In addition, patients usually have evidence of more than 1 risk factor for liver disease.[10] Recent evidence suggests that a higher number of cardiometabolic risk factors may interact with alcohol intake in individuals fulfilling MASLD or MetALD criteria, increasing the risk of significant fibrosis.[5] In addition, individuals with SLD are at elevated cardiovascular risk, which may be even greater in those with MetALD compared with MASLD, indicating a potentially additive effect of alcohol consumption alongside cardiometabolic risk factors.[11] Therefore, a comprehensive evaluation of individuals with SLD is recommended, including an assessment of metabolic dysfunction, quantification of alcohol intake, and investigation for other liver disease causes in line with current guidelines (Figure 2).[12,13] This approach could facilitate the classification into SLD subtypes and can be easily performed in different settings, including resource-limited areas.

Assessing alcohol consumption is essential in individuals with SLD to facilitate classification into SLD subtypes and inform treatment options. However, drinking patterns and alcohol use levels can fluctuate over time, and definitions of a standard drink vary internationally,[14] complicating the quantification of alcohol intake in routine clinical practice and hindering comparisons across populations. For example, the World Health Organization (WHO) defines a standard drink as containing 10 grams of pure alcohol, while the Dietary Guidelines for Americans define a standard drink as 14 grams of alcohol.[14] Thus, centers should summarize the assessment of alcohol intake using local definitions into grams per week until a universal definition of a standard drink is adopted.

There are several self-report questionnaires to screen for hazardous drinking, harmful drinking, or alcohol use disorder (AUD), including the single-question screener, National Institute on Alcohol Abuse and Alcoholism (NIAAA) Single Alcohol Use Screening Question, the CAGE 4-item questionnaire, the Alcohol Use Disorders Identification Test (AUDIT) and its concise version (AUDIT-C), among others.[15] The AUDIT is a 10-item questionnaire that was developed by the WHO. It is suitable for patients with underlying liver disease.[16] An AUDIT score $\geq$8 is considered indicative of hazardous or harmful alcohol use, whereas a cutoff of $\geq$15 suggests alcohol dependence. AUDIT-C includes the first 3 questions of AUDIT that are related to quantity-frequency measures, and scores over 4 in males and 3 in females can identify hazardous drinking. Due to their simplicity and widespread use, the AUDIT or AUDIT-C should be used to screen for AUD or hazardous drinking in all patients with SLD, respectively. Additionally, individuals with a history of AUD should be assessed for MetALD or ALD, even when reporting current alcohol intake below 140 or 210 grams/week for females and males, respectively. The timeline follow-back (TLFB) questionnaire is another retrospective, calendar-based method used to assess daily alcohol intake during the last 7 to 30 days. Although TLFB is considered the gold standard to assess alcohol consumption, it can be time-consuming and does not capture lifetime alcohol exposure.[17] Particular attention should be given to those with a history of AUD, health or social consequences of alcohol use, history of binge drinking, or consistent alcohol consumption exceeding 140 and 210 grams per week for females and males in the past, respectively.

Self-reported questionnaires may underestimate alcohol consumption in patients with SLD.[18] The AUDIT and AUDIT-C questionnaires have lower sensitivity in detecting alcohol use compared with alcohol biomarkers, highlighting the need for incorporating alcohol biomarkers into routine clinical practice for a more accurate assessment of recent alcohol consumption.[18] Non-oxidative products of alcohol metabolism, such as ethyl glucuronide, ethyl sulfate, ethyl phosphate, phosphatidylethanol (PEth), and fatty-acid ethyl esters, may facilitate identification of alcohol use in SLD.[19] Other potential indirect indicators of alcohol use may include carbohydrate-deficient transferrin, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio $>$2, elevated mean corpuscular volume, and gamma-glutamyl transpeptidase.[20] However, these tools should be used cautiously, as liver enzymes elevations are non-specific, do not replace a thorough clinical history and interview, and are not yet validated for a MetALD diagnosis. These gaps also emphasize the importance of training hepatology providers to better quantify alcohol use and screen for AUD in clinical practice.

PEth is a blood-based biomarker and appears to be the most promising and clinically useful test to identify individuals at risk of MetALD.[21] PEth is not significantly influenced by sex or body mass index (BMI) and provides an estimate of alcohol consumption over the past 1 to 3 weeks, although its use is optimal for ruling out moderate drinking above social drinking and ruling in excessive drinking. However, PEth levels may be falsely

Table 2. Summary of Recommendations for the Different Clinical Aspects of MetALD

Number	Recommendations
Clinical assessment of patients with suspected MetALD	
1	In individuals with steatotic liver disease, routine primary care screening for metabolic risk factors, including excess weight, abdominal obesity, prediabetes or diabetes, arterial hypertension, and dyslipidemia should be performed regardless of the levels of alcohol use.
2	Alcohol use should be quantified in all individuals with suspected SLD, including quantification of extended periods of daily drinking or drinking above 7 to 14 standard drinks per week, current levels of alcohol use (past 2 weeks, average drinking per week for the past 3 to 6 months), and drinking patterns.
3	The AUDIT or the AUDIT-C version should be used to screen for AUD in all patients with SLD.
4	Direct biomarkers of alcohol use (ie, PEth, ethyl glucuronide, or ethyl sulfate) could facilitate the identification of individuals with significant levels of recent alcohol use (3 days to 2 months, depending on technique).
5	Alcohol use should be quantified in grams per week. Thus, each center should tailor the assessment of alcohol using the local definitions of standard drinks, recommendations, and guidelines.
6	In individuals with significant alcohol use and abnormal fasting glucose, elevated arterial blood pressure, excess weight, and/or abnormal serum cholesterol or triglycerides, cardiometabolic risk factors and liver disease should be reassessed after a period of >8 to 12 weeks of abstinence or reduced drinking if possible. This is to identify alcohol vs cardiometabolic risk as the originating driver of the individual's disease.
7	In the presence of metabolic dysfunction, prior history of alcohol use should be thoroughly assessed in individuals with suspected SLD. Particular attention should be given to those with a history of AUD, health or social consequences from alcohol use, history of binge drinking, or consistent alcohol consumption exceeding 140 and 210 grams per week for females and males in the past, respectively.
8	In individuals with lean SLD (without visceral adiposity) and no significant improvements in liver enzymes after the management of metabolic dysfunction and alcohol abstinence, undisclosed alcohol use should be considered along with other causes of liver abnormalities.
9	Individuals with a history of AUD should be assessed for MetALD or ALD, even when they report a current alcohol intake of less than 140 to 210 grams/week for females and males, respectively.
10	Routine liver biopsy is not necessary to diagnose MetALD. However, it can be considered to rule out other potential differential diagnoses in case of clinical doubt.
Natural history and progression of MetALD	
11	Patients with suspected MetALD should be assessed to identify the presence of liver fibrosis and advanced chronic liver disease at diagnosis.
12	Patients with MetALD should undergo the assessment of leading risk factors for progression, including current levels of alcohol use, dietary patterns, physical activity, and family history of advanced fibrosis or advanced chronic liver disease due to SLD.
13	Standardized protocols should be implemented to assess lifetime alcohol use, utilizing validated questionnaires and biomarkers to ensure accurate and consistent identification of ALD.
14	Noninvasive assessment of liver disease, including surrogate markers of steatohepatitis and fibrosis, should be performed over time to identify responses to control of metabolic dysfunction and cessation of alcohol use.
15	PEth, ethyl glucuronide, and/or ethyl sulfate may be used for follow-up alcohol consumption in patients with MetALD.
16	Routine evaluation of anthropometric features (ie, weight, height, waist circumference, and BMI) and metabolic biomarkers, including fasting glucose, HbA1c, and lipid profiles, is essential for the comprehensive assessment of MetALD.
Noninvasive biomarkers and risk stratification in MetALD	
17	Noninvasive markers validated in MASLD and ALD should be used in MetALD to estimate steatosis and stage fibrosis. However, specific performance should be prospectively assessed in further studies including patients with MetALD exclusively.
18	Genetic polymorphisms (ie, *PNPLA3*, *TM6SF2*, or *HSD17B13*) testing should be considered on a case-by-case basis, especially in those individuals with uncertain risk of liver disease progression.
Comprehensive management strategies	
19	Health systems should advocate for a comprehensive approach to MetALD management, including multiple professionals such as hepatologists, gastroenterologists, endocrinologists, dietitians, and mental health professionals.
20	Structured lifestyle modifications are important for MetALD management, including reduction/cessation of alcohol intake, weight loss, and exercise.
21	Pharmacotherapy options, such as weight loss therapies, could be considered in patients with MetALD based on individual patient profiles where available and indicated.
Clinical trials and gaps of knowledge	
22	Standardized research protocols for patients with SLD who drink alcohol in excess should be performed, including clear selection criteria and well-defined endpoints, to ensure consistency and comparability across studies.
23	Patients with SLD and evidence of significant fibrosis who are unable to stop consuming moderate amounts of alcohol, despite documented professional advice as to its consequences to their health, should be considered as having AUD.
24	Longitudinal studies should be promoted to better understand the natural history and progression of MetALD, including a proper assessment of alcohol at baseline and use during the study period.
25	The pathophysiological mechanisms of MetALD should be identified and prioritized in research to uncover potential therapeutic targets.

Table 2. Continued

Number	Recommendations
26	Studies focusing on the interaction between genetic predispositions and environmental factors in the development of MetALD are necessary to conduct a precision medicine approach.
27	Research exploring novel diagnostic tools and noninvasive imaging techniques for early detection and monitoring of MetALD is necessary.
28	Clinical trials could include individuals diagnosed with mild AUD. However, the management of alcohol intake should follow best practices in all trials in MetALD.

ALD, alcohol-associated liver disease; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; AUDIT-C, Alcohol Use Disorders Identification Test-Concise; BMI, body mass index; HbA1c, glycated hemoglobin; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; MetALD, metabolic dysfunction- and alcohol-associated liver disease; PEth, phosphatidylethanol; PNPLA3, patatin-like phospholipase domain 3; SLD, steatotic liver disease; TM6SF2, transmembrane 6 superfamily member 2.

low in the presence of hemolysis, which may be present in patients with alcohol-associated hepatitis and cirrhosis.[22] A PEth cutoff of $<$20 ng/mL is usually used to rule out alcohol use, whereas a PEth $\geq$200 ng/mL rule in harmful alcohol use.[23] In the setting of a randomized trial of patients with SLD and a self-reported history of excessive alcohol use, PEth correlates moderately well with self-reported weekly alcohol intake.[24] PEth may be useful if there are concerns regarding MetALD, but the self-report suggests a level of alcohol consumption that is in a borderline zone between MASLD and MetALD. It may also be used to confirm MetALD given the range of alcohol consumption may vary within the MetALD category from 2 to 3 drinks per day to 5 to 6 drinks per day. Direct biomarkers of alcohol use in combination with self-report could thereby facilitate the identification of individuals with significant levels of recent alcohol use (3 days to 2 months, depending on technique) and should be considered according to local availability (Figure 2).[23]

Alcohol use may directly influence each of the 5 metabolic risk factors included in the metabolic dysfunction definition.[25] Of note, the interaction between metabolic dysfunction and alcohol use can result in liver injury in at least an additive manner. However, alcohol can contribute to excess weight due to the caloric content of beverages and links to unhealthy eating.[26] In addition, alcohol use is associated with high blood pressure, hypertriglyceridemia, and hyperglycemia, which may suggest that in some people, the role of alcohol in their SLD is overstated.[27,28] Given this interlinked relationship between metabolic dysfunction and alcohol use, we suggest that cardiometabolic risk factors and liver disease should be reassessed after a period of 8 to 12 weeks of abstinence or reduced alcohol consumption (if feasible), especially in those with isolated hypertension or hypertriglyceridemia.[23] This could identify alcohol vs cardiometabolic risk as the dominant driver of the individual's disease and provide tailored therapy.

Approximately 7% to 20% of individuals with suspected MASLD have a BMI below 25 kg/m^2. In this scenario, clinical guidelines recommend ruling out inherited or genetic disorders, lipodystrophy, drug-induced SLD, and inflammatory conditions, among other potential causes.[29] However, alcohol consumption is extremely frequent in clinical practice and the WHO have estimated the AUD prevalence at 7% globally in individuals aged over 15 years old.[30] More than 90% of individuals who engage in heavy alcohol consumption will develop steatosis, whereas liver fat content rapidly declines after

Box 1. Key Aspects in the Assessment and Management of MetALD

-Routine assessment of metabolic risk factors, including excess weight, abdominal obesity, prediabetes or diabetes, arterial hypertension, and dyslipidemia should be performed regardless of the levels of alcohol use.
-Alcohol use should be quantified, including current drinking, drinking patterns, and prior history of alcohol use using validated questionnaires.
-Direct biomarkers of alcohol use—including blood PEth— could facilitate the classification into steatotic liver disease subtypes. A PEth between 20 and 200 ng/mL suggests moderately high alcohol intake, but thresholds should be validated in multiple cohorts.
-Prior history of AUD should be thoroughly assessed in individuals with suspected SLD.
-Noninvasive markers validated in MASLD and ALD should be used in MetALD to estimate steatosis and stage fibrosis. However, specific performance should be prospectively assessed in further studies including patients with MetALD exclusively.
-Health systems should advocate for a comprehensive approach to MetALD management, involving professionals such as hepatologists, gastroenterologists, endocrinologists, dietitians, and mental health specialists.
-Structured lifestyle modifications are important for MetALD management, including reduction/cessation of alcohol intake, weight loss, and exercise.

ALD, alcohol-associated liver disease; AUD, alcohol use disorder; MetALD, metabolic dysfunction- and alcohol-associated liver disease; Peth, phosphatidylethanol; SLD, steatotic liver disease.

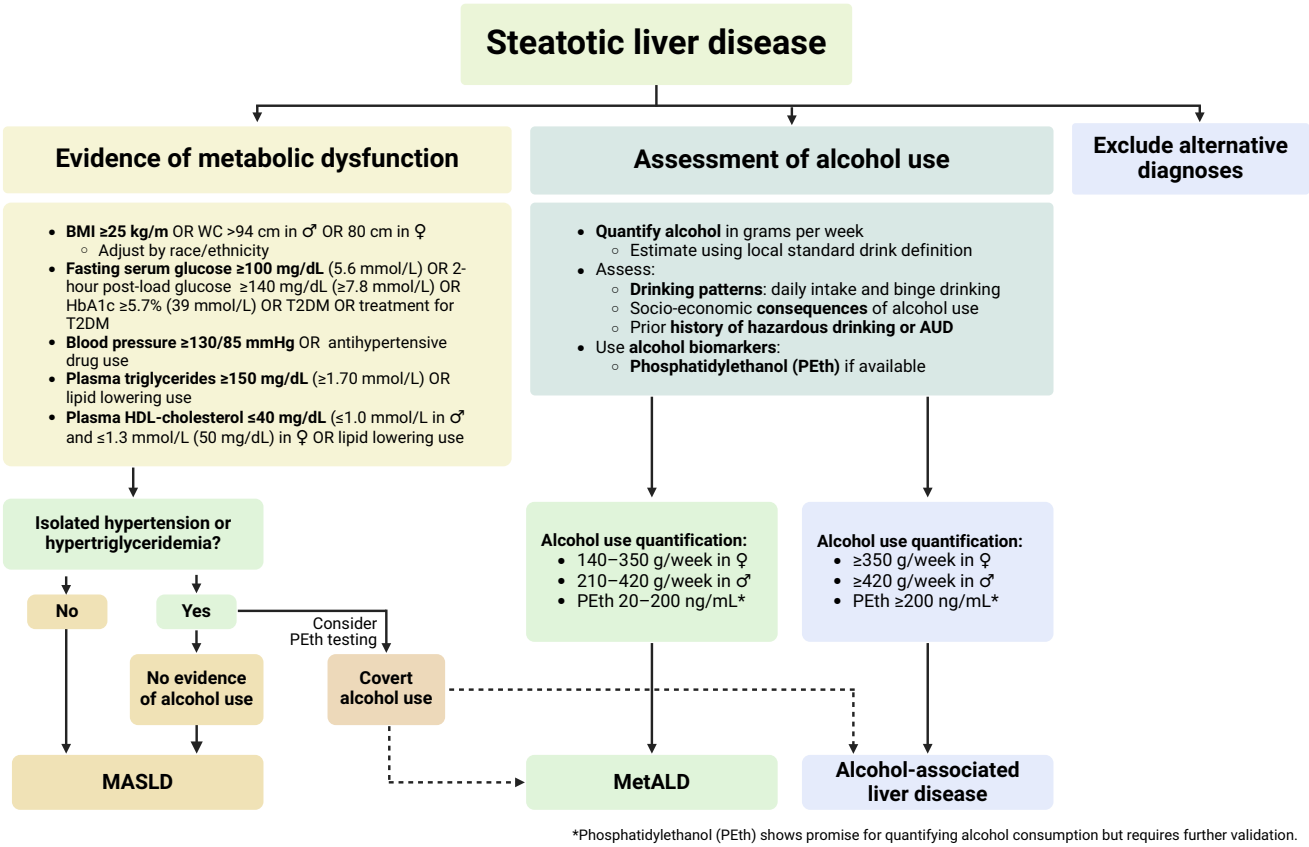

Figure 2. Recommendations for the comprehensive assessment of patients with presumed MetALD. Cutpoints for PEth require further validation in multiple prospective cohort studies over time. BMI, body mass index; HDL, high-density lipoprotein; PEth, phosphatidylethanol; T2DM, type 2 diabetes mellitus; WC, waist circumference

alcohol withdrawal.[31,32] Therefore, in individuals with lean SLD (without visceral adiposity) who show no significant improvement in liver enzymes following metabolic management and alcohol abstinence, covert alcohol use should be considered, alongside other potential causes of liver abnormalities.

Although there is substantial overlap between the histological features of ALD and MASLD, certain histologic changes are more commonly seen in alcohol-driven liver injury, including alcohol-related foamy degeneration, heavy parenchymal infiltration with many neutrophils, satellitosis, large and abundant Mallory-Denk bodies, canalicular and ductular cholestasis, and sclerosing hyaline necrosis, among others.[23] However, the absence of these histopathologic changes does not rule out alcohol-related liver injury, and studies evaluating histologic features in MetALD are lacking.[33] Liver biopsy is not exempt from limitations and potential adverse effects[34] and multiple noninvasive tests (NITs) and imaging techniques that can assess liver fibrosis, steatosis, and prognosis are readily available in clinical practice.[35,36] We consider that routine liver biopsy is not necessary for a MetALD diagnosis. However, it can be considered to rule out other potential differential diagnoses in cases of clinical uncertainty.

The Natural History and Progression of MetALD

Recommendations 11 to 16. The natural history of MetALD has not been well-characterized, and most current knowledge has been extrapolated from MASLD and ALD. Exposure to risk factors, including unhealthy lifestyles, dietary patterns, metabolic dysfunction, and alcohol use, leads to the development of steatosis and steatohepatitis. Approximately one-third of patients with MASLD will progress to liver fibrosis, and 3% to 5% will develop cirrhosis.[37] The lifetime risk for symptomatic cirrhosis in ALD is 20% to 25%.[38] In both diseases, the liver fibrosis stage and alcohol use have been consistently linked to a higher risk of liver events and mortality.[5,39–41] When comparing the SLD subtypes, alcohol-driven liver disease has shown a higher risk of liver fibrosis progression than driven by metabolic dysfunction alone.[42] Therefore, patients with suspected MetALD should be evaluated for liver fibrosis and advanced chronic liver disease at diagnosis. Patients with MetALD should undergo a thorough assessment of key risk factors for disease progression, including current alcohol consumption, dietary patterns, physical activity, and family history of advanced fibrosis or chronic liver disease, including liver cancer. Routine evaluation of

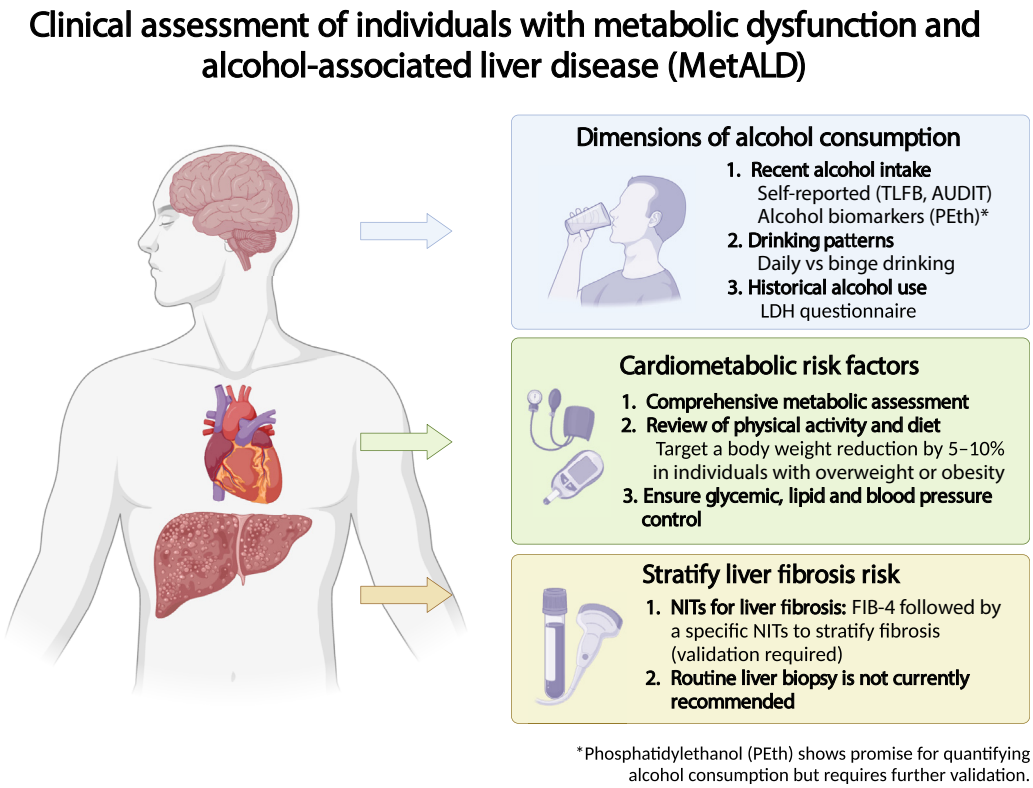

Figure 3. Main clinical aspects to consider in the assessment of patients with MetALD. LDH, lifetime drinking history.

anthropometric measures and metabolic biomarkers, including fasting glucose, glycated hemoglobin (HbA1c), and lipid profiles are essential for a comprehensive assessment of MetALD.

In terms of prognosis, individuals with MetALD may have increased all-cause, cancer, and liver-related mortality risk compared to those without SLD.[43] These risks could be more pronounced in people with MetALD and significant liver fibrosis.[43] Patients with MASLD and MetALD could also have an increased risk of cancer, particularly liver and gastrointestinal cancers.[44] A recent systematic review showed that higher levels of alcohol use increased the risk of malignancy and cancer-related mortality in patients with MetALD compared with those with MASLD.[45] In addition, a retrospective cohort study using algorithms to estimate SLD subtypes in the United Network for Organ Sharing (UNOS) registry estimated that MetALD is the third leading etiology among those waitlisted and transplanted, exhibiting worse pre- and post-transplantation outcomes compared with ALD.[46] Patients with MetALD also experienced higher waitlist removal, all-cause mortality, and graft failure compared with those with ALD.[46] Thus, the categorization into SLD subtypes is relevant to address the drivers of liver and cardiovascular disease, in addition to prognostic purposes.

As mentioned before, routine alcohol use assessments have not been systematically implemented in clinical practice across many settings. Consequently, standardized protocols should be implemented to assess lifetime alcohol use, utilizing validated questionnaires and biomarkers to ensure the accurate and consistent identification of alcohol use in the multiple dimensions: current drinking, drinking patterns (daily vs binge drinking), and prior history of alcohol consumption and AUD (Figure 3).[47] It is important to notice that alcohol use can also influence an overestimation of liver stiffness by some methods.[48] Conversely, the estimation of liver fibrosis in individuals with current alcohol use can lead to a significant reduction in levels of alcohol intake over time.[49] As alcohol cessation is a therapeutic goal, alcohol biomarkers (ie, PEth, ethyl glucuronide, and/or ethyl sulfate) may be used for follow-up assessments of alcohol consumption in patients with MetALD. We also consider that performing a noninvasive assessment of liver disease, including surrogate markers of steatohepatitis and fibrosis, should be considered over time to identify responses to control of metabolic dysfunction and alcohol cessation.

Noninvasive Biomarkers and Risk Stratification in MetALD

Recommendations 17 to 18. In recent years, risk stratification for SLD has typically relied on NITs and imaging techniques designed to identify the presence of advanced fibrosis and at-risk steatohepatitis.[50,51] In particular, current clinical guidelines from the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA), and the

European Association for the Study of the Liver (EASL) recommend the use of Fibrosis-4 (FIB-4) index and a further assessment with vibration-controlled transient elastography or another NIT to stratify risk in patients with SLD.[12,50,52,53] Recent data suggest that patients with MetALD could exhibit a significantly higher liver stiffness than those with MASLD.[54] Also, a recent study including participants from the United States with excess weight and MetALD, estimated an advanced fibrosis prevalence at 7.7% and cirrhosis at 3.9%.[55]

Currently, data on liver fibrosis stratification in MetALD is scarce. However, recent studies suggest that the performance of NITs in MetALD may be comparable to that in MASLD. For example, a cross-sectional study using magnetic resonance elastography in Korean participants found that a FIB-4 $\geq$1.3 had a sensitivity of 71.4%, a specificity of 77.3%, a positive predictive value of 4.6%, and a negative predictive value of 99.4% in MetALD.[56] Therefore, NITs validated for MASLD and ALD should be used to estimate steatosis and fibrosis stages in MetALD, whereas their specific performance should be prospectively evaluated in future studies focusing exclusively on patients with MetALD.

The assessment of inherited genetic backgrounds have also demonstrated potential clinical utility in SLD.[57] For example, the patatin-like phospholipase domain 3 (*PNPLA3*) I148M genetic variant that plays a role in hepatocyte fat metabolism has been linked to the prevalence and severity of SLD, and an increased risk of hepatocellular carcinoma (HCC).[2] Other genetic polymorphisms of clinical relevance include the transmembrane 6 superfamily member 2 (*TM6SF2*) that plays a role in cholesterol metabolism, and membrane bound O-acyltransferase domain containing 7 (*MBOAT7*) that influences phospholipid metabolism. In contrast, the loss of function allele of hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) has a protective effect.[58] Studies combining genetic polymorphisms have also demonstrated a higher SLD severity, potentially helping to better stratify liver fibrosis risk and prognosis.[59–61] Although current society guidelines do not recommend routine genetic assessment, polymorphism testing (ie, *PNPLA3*, *TM6SF2*, *MBOAT7,* or *HSD17B13*) could be considered on a case-by-case basis, especially in individuals with uncertain risk of liver disease progression.

Comprehensive Management Strategies

Recommendations 19 to 21. Effective management of MetALD requires a holistic and personalized approach that addresses both drivers of liver disease. This therapeutic strategy should be focused on lifestyle modifications, including reduction/cessation of alcohol intake, weight loss, and exercise. All patients should undergo nutritional assessment and a plan established for regular follow-up.[62] The need for more specialized obesity management, including additional cardiology or metabolic support, psychological support, pharmacological therapies, and bariatric surgery referral, should be evaluated on an individual basis, taking into account local availability, resources, and comorbidities.

Currently there are no approved pharmacological therapies for the management of MetALD nor United States Food and Drug Administration nor European Medicines Agency guidance regarding clinical drug development and approval in this newly formed entity. Therefore, prioritizing alcohol abstinence or reducing alcohol consumption should be the first step, followed by intensive lifestyle interventions to induce weight loss and reduce high carbohydrate and high cholesterol consumption, and incorporating regular moderate-intensity exercise in a weekly routine. Health systems should advocate for a comprehensive approach to MetALD management, including multiple professionals such as hepatologists, gastroenterologists, endocrinologists, dietitians, and mental health professionals.

Incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists, are transforming obesity treatment and show potential in reducing alcohol consumption, making them promising for MetALD management.[63] For instance, a recent phase III clinical trial of semaglutide 2.4 mg weekly vs placebo has demonstrated that semaglutide improves MASH resolution without worsening fibrosis and also improves liver fibrosis at 72 weeks.[64] Resmetirom, a thyroid hormone receptor beta agonist, has shown significant benefits in MASH resolution, fibrosis improvement, and lipid profile enhancement, with similar efficacy in patients with and without alcohol use markers.[65] Furthermore, the gut-brain and gut-liver axes play key roles in chronic liver disease, presenting gut microbiota modulation as a novel therapeutic avenue.[63] For example, a phase I placebo-controlled trial showed that 1 fecal microbiota transplantation enema was safe in patients with cirrhosis and reduced alcohol cravings and consumption using objective biomarkers.[66] Finally, fibroblast growth factor 21 is a liver-brain axis hormone governing energy homeostasis that also modulates alcohol intake/preference and other substances, offering an additional therapeutic target for future clinical trials in MetALD.[67]

Clinical Trials and Gaps of Knowledge

Recommendations 22 to 28. The 2023 definition of MetALD identifies important gaps in our knowledge and poses significant challenges in diagnostic and therapeutic approaches (Box 2).[3] Work is needed to overcome limitations in the current definition concerning self-reported alcohol consumption, the influence of alcohol in metabolic dysfunction, and measures for alcohol exposure over time can make identification of MetALD difficult.[68] As of yet, there are limited data on NITs and endpoints in MetALD that can inform clinical trial design.[69,70]

Box 2. Unmet Needs and Research Priorities in MetALD

-Establish and validate clear selection criteria and well-defined endpoints in clinical trials to ensure consistency and comparability across studies.
-Reevaluate the diagnostic criteria for AUD in individuals with MetALD.
-Conduct longitudinal studies to better understand the natural history and progression of MetALD, including comprehensive assessments of alcohol use at baseline and during the study period.
-Investigate the pathophysiological mechanisms of MetALD to identify potential therapeutic targets.
-Perform studies focusing on the interaction between genetic predispositions and environmental factors in MetALD development to enable precision medicine approaches.
-Explore novel diagnostic tools and noninvasive imaging techniques for the early detection and monitoring of MetALD.
- Incorporate PEth and other alcohol biomarkers into clinical practice, while validating threshold levels of PEth to differentiate between MASLD, MetALD, and ALD.

ALD, alcohol-associated liver disease; AUD, alcohol use disorder; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction- and alcohol-associated liver disease; PEth, phosphatidylethanol.

Taken together, these hinder the consistency and comparability of clinical trials and observational studies. To address these limitations, standardized research protocols for patients with SLD and increased alcohol use of recommended limits should be agreed upon and implemented, with clear selection criteria, well-defined endpoints, and approaches to assess liver disease severity, alcohol intake, and metabolic risk factors. Patients with the psychiatric syndrome of AUD should have access to addiction specialists with integration of behavioral therapies and should not be excluded from clinical trials based on mild AUD alone. When patients with mild AUD are included in MetALD trials, the management of alcohol intake should follow best practices and be carefully documented. Additionally, health care providers should play an active role in the screening and treatment of patients with AUD.

A recent study performed a head-to-head comparative efficacy analysis and demonstrated that PEth is both clinically and statistically superior to other indirect biomarkers of alcohol use in differentiating SLD subtypes.[71] The interplay between metabolic dysfunction, alcohol-induced liver injury, inflammation, and fibrosis is complex and not fully understood.[1] Therefore, the pathophysiological mechanisms of MetALD should be identified and prioritized in research to uncover potential therapeutic targets. Research should also focus on exploring novel diagnostic tools and noninvasive imaging techniques for the early detection and monitoring of MetALD. Genetic variations, such as polymorphisms in genes related to lipid metabolism, alcohol metabolism, and fibrogenesis, may influence susceptibility to liver damage and response to treatment[1] in concert with environmental and lifestyle factors like diet and alcohol consumption. This new knowledge could enable personalized risk assessment and tailored therapeutic strategies.

Conclusions

MetALD is a condition that combines 2 of the leading causes of chronic liver disease. The natural history has not yet been adequately characterized, and it remains unclear whether MetALD poses a differential risk of adverse outcomes. However, key evidence from cohort studies and other liver diseases, such as MASLD and ALD, can help guide decision-making in times of uncertainty. The current Delphi process has consistently shown that thorough characterization of alcohol consumption is essential. Biomarkers such as PEth may be able to help classify individuals into different SLD subtypes, but more data is needed. Standardized clinical trial designs using simple but robust NITs and endpoints will generate meaningful new evidence in the MetALD field.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.02.017.

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Correspondence
Address correspondence to: Rohit Loomba, MD, MHSc, Professor of Medicine, Chief, Division of Gastroenterology and Hepatology, Director, MASLD Research Center, Adjunct Professor, Division of Epidemiology, 1W202 ACTRI Building # MC0887, 9452 Medical Center Drive, University of California at San Diego, La Jolla, California 92093-0887. e-mail: roloomba@ucsd.edu.

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CRediT Authorship Contributions
Luis Antonio Diaz, MD (Formal analysis: Equal; Writing – original draft: Lead; Writing – review & editing: Lead)
Veeral Ajmera, MD (Writing – review & editing: Equal)
Juan Pablo Arab, MD (Writing – review & editing: Equal)
Daniel Huang, MD (Writing – review & editing: Equal)
Cynthia Hsu, MD, PhD (Writing – review & editing: Equal)
Brian P. Lee, MD (Writing – review & editing: Equal)
Alexandre Louvet, MD, PhD (Writing – review & editing: Equal)
Maja Thiele, MD, PhD (Writing – review & editing: Equal)
Federica Tavaglione, MD, PhD (Writing – review & editing: Equal)
Monica Tincopa, MD (Writing – review & editing: Equal)

Elisa Pose, MD, PhD (Writing – review & editing: Equal)
Leon A. Adams, MD, PhD (Writing – review & editing: Equal)
William Alazawi, MD, PhD (Writing – review & editing: Equal)
Marco Arrese, MD (Writing – review & editing: Equal)
Ramon Bataller, MD, PhD (Writing – review & editing: Equal)
Ajay Duseja, MD (Writing – review & editing: Equal)
Suthat Liangpunsakul, MD (Writing – review & editing: Equal)
Michael R. Lucey, MD (Writing – review & editing: Equal)
Philippe Mathurin, MD, PhD (Writing – review & editing: Equal)
Jessica Mellinger, MD (Writing – review & editing: Equal)
Atsushi Nakajima, MD, PhD (Writing – review & editing: Equal)
Vlad Ratziu, MD, PhD (Writing – review & editing: Equal)
Nancy Reau, MD (Writing – review & editing: Equal)
Mary E. Rinella, MD (Writing – review & editing: Equal)
Mark Thursz, MD (Writing – review & editing: Equal)
Vincent Wai-Sun Wong, MD (Writing – review & editing: Equal)
Patrick S. Kamath, MD (Writing – review & editing: Equal)
Rohit Loomba, MD, MHSc (Conceptualization: Equal; Supervision: Equal; Writing – review & editing: Equal)

Conflicts of interest

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Supplementary Table 1. Statements and Agreement Degree (Ranging From 1 [Strongly Disagree] to 5 [Strongly Agree]) in the First Delphi Round

Statements	Agreement (R1) Median (IQR)	SD
Clinical assessment of patients with suspected MetALD		
In individuals with SLD, routine screening for metabolic risk factors, including excess weight, abdominal obesity, prediabetes or diabetes, arterial hypertension, and dyslipidemia should be performed regardless of the levels of alcohol use.	5 (5–5)	0.00
Alcohol use should be quantified in all individuals with suspected SLD, including quantification of extended periods of daily drinking or drinking above 7 to 14 standard drinks per week, current levels of alcohol use (past 2 weeks, average drinking per week for the past 3 to 6 months), and drinking patterns.	5 (5–5)	0.36
The AUDIT or the AUDIT-C should be used to screen for alcohol use disorder in all patients with SLD.	5 (4–5)	0.57
Direct biomarkers of alcohol use (ie, PEth, ethyl glucuronide, or ethyl sulfate) can facilitate the identification of individuals with significant levels of recent alcohol use (3 days to 2 months, depending on technique).	5 (4–5)	0.62
Alcohol use should be quantified in grams per week. Thus, each center should tailor the assessment of alcohol using the local definitions of standard drinks, recommendations, and guidelines.	5 (4–5)	0.89
In individuals with significant alcohol use and abnormal fasting glucose, elevated arterial blood pressure, and/or abnormal serum cholesterol or triglycerides, cardiometabolic risk factors should be reassessed after a period of >8 to 12 weeks of abstinence or reduced drinking if possible. This is to identify alcohol vs cardiometabolic risk as the originating driver of the individual's disease.	4 (4–5)	0.88
In the presence of metabolic dysfunction, prior history of alcohol use should be thoroughly assessed in individuals with suspected SLD. Particular attention should be given to those with a history of AUD, health or social consequences from alcohol use, history of binge drinking, or consistent alcohol consumption exceeding 2 and 3 standard drinks per day for females and males in the past, respectively	5 (5–5)	0.48
Individuals with lean MetALD and lack of response to treatment should be tested for monogenic diseases (ie, lysosomal acid lipase deficiency, hypobetalipoproteinemia, alpha-1-antitrypsin deficiency) and consider covert alcohol use.	4 (3–5)	1.06
In case of diagnostic doubt regarding the underlying etiology, a liver biopsy may help to discriminate between metabolic- and alcohol-driven liver disease, as well as other potential differential diagnoses.	4 (2–5)	1.42
Natural history and progression of MetALD		
All patients with suspected MetALD should be assessed to identify the presence of liver fibrosis and advanced chronic liver disease at diagnosis.	5 (5–5)	0.19
Patients with MetALD should undergo the assessment of leading risk factors for progression, including current levels of alcohol use, dietary patterns, physical activity, and family history of advanced fibrosis or advanced chronic liver disease due to SLD.	5 (5–5)	0.36
If available, genetic polymorphisms (ie, PNPLA3, TM6SF2, SERPINA1, and HSD17B13) can be assessed to stratify the risk of progression, especially in those individuals with uncertain risk.	4 (3–4)	0.88
Standardized protocols should be implemented to assess lifetime alcohol use, utilizing validated questionnaires and biomarkers to ensure accurate and consistent identification of ALD.	5 (4–5)	0.80
Steatohepatitis and fibrosis should be assessed over time to identify responses to control of metabolic dysfunction and cessation of alcohol use.	5 (5–5)	0.40
Biomarkers for MetALD		
Well-known noninvasive markers validated in MASLD and ALD should be used in MetALD to estimate steatosis and stage fibrosis. However, specific performance should be prospectively assessed in further studies including patients with MetALD exclusively.	5 (4–5)	0.64
Cutoffs and interpretation for PEth, ethyl glucuronide, and/or ethyl sulfate should be standardized before they can be recommended for routine assessment of recent alcohol consumption in patients with MetALD.	5 (3–5)	1.47
Routine evaluation of anthropometric features (ie, weight, height, waist circumference, and BMI) and metabolic biomarkers, including fasting glucose, HbA1c, and lipid profiles, is essential for the comprehensive assessment of MetALD.	5 (4–5)	0.45

Supplementary Table 1. Continued

Statements	Agreement (R1) Median (IQR)	SD
Comprehensive management strategies		
Health systems should advocate for a multidisciplinary approach to MetALD management, including hepatologists, gastroenterologists, endocrinologists, dietitians, and mental health professionals.	5 (5–5)	0.59
Lifestyle modifications are important for MetALD management, including alcohol cessation, weight loss, and exercise.	5 (5–5)	0.27
Pharmacotherapy options, such as the use of anti-fibrotic agents or weight loss therapies could be considered in patients with MetALD based on individual patient profiles.	5 (4–5)	0.80
Consider surgical interventions, such as bariatric surgery, in patients with severe obesity and MetALD who do not respond to conventional therapies. However, careful screening for substance use and comorbid mental health disorders should be undertaken as part of the preoperative risk assessment.	4 (3–5)	1.00
Clinical trials and gaps of knowledge		
Standardized research protocols for patients with SLD who drink alcohol in excess should be performed, including clear selection criteria and well-defined endpoints, to ensure consistency and comparability across studies.	5 (5–5)	0.19
The use of longitudinal studies should be promoted to better understand the natural history and progression of MetALD, including a proper assessment of alcohol at baseline and use during the study period.	5 (5–5)	0.00
The pathophysiological mechanisms of MetALD should be identified and prioritized in research to uncover potential therapeutic targets.	5 (5–5)	0.53
Studies focusing on the interaction between genetic predispositions and environmental factors in the development of MetALD are necessary to conduct a precision medicine approach.	5 (4–5)	0.54
Research exploring novel diagnostic tools and noninvasive imaging techniques for early detection and monitoring of MetALD is necessary.	5 (4–5)	0.75
Clinical trials could include individuals diagnosed with mild AUD. However, the management of alcohol intake should follow best practices in all trials in MetALD.	5 (4–5)	0.56

ALD, alcohol-associated liver disease; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; AUDIT-C, Alcohol Use Disorders Identification Test Concise; BMI, body mass index; HbA1c, glycated hemoglobin; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; IQR, interquartile range; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction- and alcohol-associated liver disease; PEth, phosphatidylethanol; PNPLA3, patatin-like phospholipase domain 3; R1, round 1; SD, standard deviation; SLD, steatotic liver disease; TM6SF2, transmembrane 6 superfamily member 2.

Supplementary Table 2. Statements and Agreement Degree (Ranging From 1 [Strongly Disagree] to 5 [Strongly Agree]) in the Second Delphi round, and Response Stability Between the First Round and the Second Round

	Agreement (R1)		Stability between R1 and R2	
Statements	Median (IQR)	SD	Z	*P*-value
Clinical assessment of patients with suspected MetALD				
In individuals with SLD, routine screening for metabolic risk factors, including excess weight, abdominal obesity, prediabetes or diabetes, arterial hypertension, and dyslipidemia should be performed regardless of the levels of alcohol use.	5 (5–5)	0.00	–	1.000
Alcohol use should be quantified in all individuals with suspected SLD, including quantification of extended periods of daily drinking or drinking above 7 to 14 standard drinks per week, current levels of alcohol use (past 2 weeks, average drinking per week for the past 3 to 6 months), and drinking patterns.	5 (4–5)	0.46	1.000	.508
The AUDIT or the AUDIT-C version should be used to screen for alcohol use disorder in all patients with steatotic liver disease.	5 (4–5)	0.72	−0.386	1.000
Direct biomarkers of alcohol use (ie, PEth, ethyl glucuronide, or ethyl sulfate) can facilitate the identification of individuals with significant levels of recent alcohol use (3 days to 2 months, depending on technique).	5 (5–5)	0.53	−0.816	.688
Alcohol use should be quantified in grams per week. Thus, each center should tailor the assessment of alcohol using the local definitions of standard drinks, recommendations, and guidelines.	5 (4–5)	0.72	−0.399	.781
In individuals with significant alcohol use and abnormal fasting glucose, elevated arterial blood pressure, and/or abnormal serum cholesterol or triglycerides, cardiometabolic risk factors and liver disease should be reassessed after a period of >8 to 12 weeks of abstinence or reduced drinking if possible. This is to identify alcohol vs cardiometabolic risk as the originating driver of the individual's disease.	4.5 (4–5)	0.65	−1.361	.313
In the presence of metabolic dysfunction, prior history of alcohol use should be thoroughly assessed in individuals with suspected SLD. Particular attention should be given to those with a history of AUD, health or social consequences from alcohol use, history of binge drinking, or consistent alcohol consumption exceeding 2 and 3 standard drinks per day for females and males in the past, respectively	5 (5–5)	0.41	0.000	1.000
In individuals with lean SLD (without visceral adiposity) and no significant improvements in liver enzymes after the management of metabolic dysfunction and alcohol abstinence, covert alcohol use should be considered along with other causes of liver abnormalities.	5 (4.5–5)	0.64	−3.280	.001
Individuals with a history of AUD should be assessed for MetALD or ALD, even when they report a current alcohol intake within the range of MASLD.	5 (4.5–5)	0.77	–	-
Routine liver biopsy is not necessary to diagnose MetALD. However, it can be considered in case of clinical doubt to rule out other potential differential diagnoses.	5 (5–5)	0.41	−3.529	.0002
Natural history and progression of MetALD				
All patients with suspected MetALD should be assessed to identify the presence of liver fibrosis and advanced chronic liver disease at diagnosis.	5 (5–5)	0.00	−1.000	1.000
Patients with MetALD should undergo the assessment of leading risk factors for progression, including current levels of alcohol use, dietary patterns, physical activity, and family history of advanced fibrosis or advanced chronic liver disease due to SLD.	5 (5–5)	0.38	0.000	1.000
Genetic polymorphisms (ie, PNPLA3, TM6SF2, or HSD17B13) testing should be considered on a case-by-case basis, especially in those individuals with uncertain risk of liver disease progression.	4 (3.5–5)	1.00	−1.857	.0963
Standardized protocols should be implemented to assess lifetime alcohol use, utilizing validated questionnaires and biomarkers to ensure accurate and consistent identification of ALD.	5 (4.5–5)	0.71	−1.446	.234
Steatohepatitis and fibrosis should be assessed over time to identify responses to control of metabolic dysfunction and cessation of alcohol use.	5 (5–5)	0.41	0.000	1.000
Biomarkers for MetALD				
Well-known noninvasive markers validated in MASLD and ALD should be used in MetALD to estimate steatosis and stage fibrosis. However, specific performance should be prospectively assessed in further studies including patients with MetALD exclusively.	5 (4–5)	0.56	−0.447	1.000
Low PEth, ethyl glucuronide, and/or ethyl sulfate may be used for follow-up alcohol consumption in patients with MetALD.	5 (4–5)	0.78	−1.384	.171
	5 (5–5)	0.38	−1.732	.250

Supplementary Table 2. Continued

Statements	Agreement (R1)		Stability between R1 and R2	
	Median (IQR)	SD	Z	*P*-value
Routine evaluation of anthropometric features (ie, weight, height, waist circumference, and BMI) and metabolic biomarkers, including fasting glucose, HbA1c, and lipid profiles, is essential for the comprehensive assessment of MetALD.				
Comprehensive management strategies				
Health systems should advocate for a comprehensive approach to MetALD management, including multiple professionals such as hepatologists, gastroenterologists, endocrinologists, dietitians, and mental health professionals.	5 (5–5)	0.34	−2.000	.125
Structured lifestyle modifications are important for MetALD management, including reduction/cessation of alcohol intake, weight loss, and exercise.	5 (5–5)	0.00	−1.414	.5000
Pharmacotherapy options, such as the use of anti-fibrotic agents or weight loss therapies could be considered in patients with MetALD based on individual patient profiles where available and indicated.	5 (4–5)	0.88	0.670	.678
Bariatric surgery could be considered in patients with severe obesity and MetALD who do not respond to conventional therapies on a case-by-case basis. However, careful screening for substance use and comorbid mental health disorders should be undertaken as part of the preoperative risk assessment due to the potential increase of addictive behaviors after surgery.	4 (5–5)	0.87	−1.334	.198
Clinical trials and gaps of knowledge				
Standardized research protocols for patients with SLD who drink alcohol in excess should be performed, including clear selection criteria and well-defined endpoints, to ensure consistency and comparability across studies.	5 (5–5)	0.34	1.000	.625
Patients with SLD and evidence of liver fibrosis who are unable to stop consuming moderate amounts of alcohol, despite its deleterious effects on their health, should be considered as having AUD.	5 (4–5)	0.79	–	-
The use of longitudinal studies should be promoted to better understand the natural history and progression of MetALD, including a proper assessment of alcohol at baseline and use during the study period.	5 (5–5)	0.29	1.414	.500
The pathophysiological mechanisms of MetALD should be identified and prioritized in research to uncover potential therapeutic targets.	5 (5–5)	0.39	0.000	1.000
Studies focusing on the interaction between genetic predispositions and environmental factors in the development of MetALD are necessary to conduct a precision medicine approach.	5 (5–5)	0.34	−1.342	.375
Research exploring novel diagnostic tools and noninvasive imaging techniques for early detection and monitoring of MetALD is necessary.	5 (4–5)	0.45	–0.060	1.000
Clinical trials could include individuals diagnosed with mild AUD. However, the management of alcohol intake should follow best practices in all trials in MetALD.	5 (4–5)	0.71	0.060	1.000

ALD, alcohol-associated liver disease; AUD, alcohol use disorder; AUDIT, Alcohol Use Disorders Identification Test; AUDIT-C, Alcohol Use Disorders Identification Test Concise; BMI, body mass index; HbA1c, glycated hemoglobin; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; IQR, interquartile range; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction- and alcohol-associated liver disease; PEth, phosphatidylethanol; PNPLA3, patatin-like phospholipase domain 3; R1, round 1; R2, round 2; SD, standard deviation; SLD, steatotic liver disease; TM6SF2, transmembrane 6 superfamily member 2.