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Metabolic and alcohol-associated liver disease (MetALD): a representation of duality

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MetALD is a recently coined term that refers to a systemic entity to describe patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and simultaneous moderate alcohol consumption. The deleterious association of alcohol and metabolic risk factors synergistically increases the development of steatohepatitis, fibrosis, and hepatocellular carcinoma (HCC). Despite its increasing incidence, the pathophysiological mechanisms triggering liver damage in MetALD remain unclear. This review aims to summarize the prevalence, pathophysiology of MetALD, taking into account the latest clinical and translational aspects.

Lately, a worldwide initiative led by major pan-national liver organizations has been undertaken to rename non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)[1,2]. The new names for MASLD and MASH, respectively, stand for metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis.

The changes are being implemented for highly legitimate reasons. Medical terminology that is felt to be "stigmatizing" should be clear steered of, regardless of its original accuracy and lack of negativity. Replacing "fatty" with "steatotic" employs a shift towards medical terminology, which is likely to increase recognition and understanding among a wider audience. Additionally, the updated terminology demonstrates a better understanding of the underlying pathophysiology of the disease as metabolic dysfunction is central to the disease pathogenesis.

According to Delphi consensus, MASLD is diagnosed when hepatic steatosis is present along with at least one of five cardiometabolic risk factors (MRF)[3]. Importantly, the Delphi panel has defined and outlined a group that has not been studied before – metabolic dysfunction and alcohol associated/related liver disease (MetALD) to represent patients with MASLD and mild alcohol consumption. The patients with MetALD consume on a weekly basis 140–350 g of alcohol for females and 210–420 g for males respectively. Correspondingly, average daily alcohol consumption varies between 20–50 g for females and 30–60 g for males[2,4]. While measuring the amount of alcohol consumed in grams per day or week may be more accurate, it can be challenging and time-consuming to obtain this information. Widely, patients struggle to remember the types and quantities of drinks they have consumed (Fig. 1). As a result, it might be beneficial to define MetALD based on the quantity of drinks consumed. Nevertheless, there has been a significant inconsistency in defining what constitutes a "drink" in terms of alcohol grams[5]. Dietary guidelines for Americans[6,7] and Latin American Association for the Study of the Liver (ALEH)[8] define a standard drink of "pure" alcohol as 14 g. According to the British Association for the Study of the Liver/British Society of Gastroenterology (BASL/BSG)[9], single standard drink of "pure" alcohol equates to 8 g. While EASL[10] and WHO[11] standardized it to 10 g to make comparisons among studies easier.

Alcohol-associated Liver Disease (ALD) is a distinct specific liver condition classified within the steatotic liver disease (SLD) group[12]. Importantly, MetALD differs from ALD based on the quantity of alcohol consumed[13]. Hence MetALD patients are at the intersection of MASLD and ALD, it is obvious that within the MetALD group the contribution of MASLD and ALD will vary. There might be cases where MASLD is seen as the predominant factor while in other patients, ALD is seen as the main influencing factor. Nevertheless, this perception could potentially shift in the future[2].

In general, MetALD is a grey area in the hepatology field with a huge unmet need for preclinical and clinical studies and there are many urgent questions that require to be answered. This review discusses the latest information on MetALD, including its prevalence, pathogenesis, translational aspects and potential therapeutic interventions to investigate previously unexplored areas and enhance our knowledge of medical needs that are not being met.

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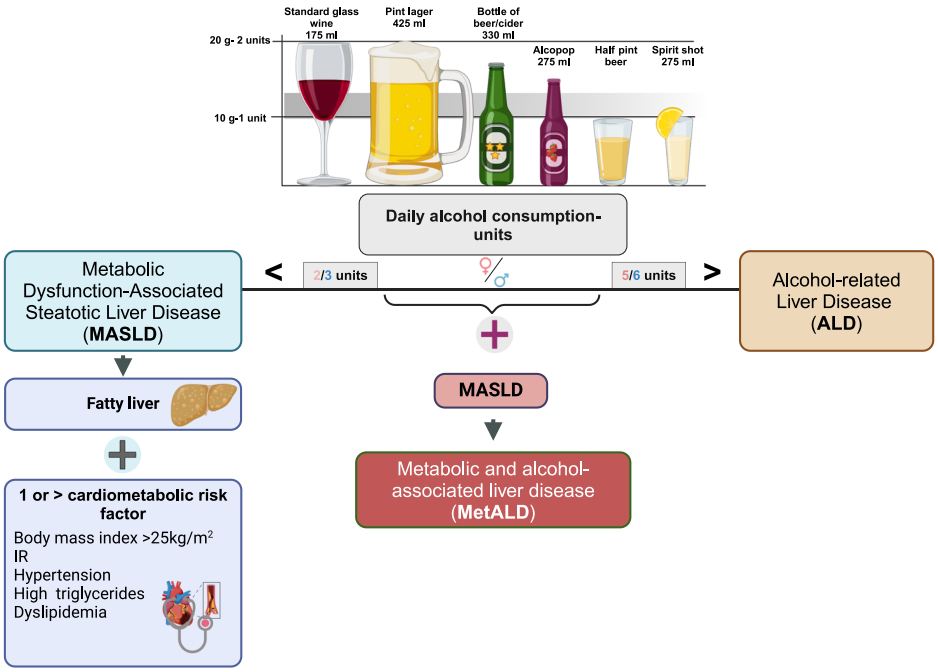

Fig. 1 | MetALD definition. According to EASL and WHO a unit of "pure" alcohol corresponds to 10 g of ethanol, which can be the amount contained in a half pint beer or a spirit shot. A standard glass of wine or a pint lager will be equivalent to 2 alcohol units. A daily alcohol consumption of 2–5 units for woman or 3–6 units for men will trigger MetALD in patients with MASLD (fatty liver plus at least one cardio-metabolic risk factor) due to bad dietary habits. Created with BioRender.

Unveiling the prevalence

Beside the rising obesity rates, over half of the world's alcohol is consumed by people living in Europe, the Americas, and the Western Pacific Region[14]. With 73.9% of Europeans consuming alcohol (8.4% of them daily)[15] and around 53% of patients being overweight or obese[16,17], is highly probable that many individuals experience an overlap between poor dietary habits and alcohol consumption. Moreover, it is common for people to combine high-calorie meals with moderate and regular alcohol consumption. In fact, despite containing seven calories per gram, alcohol doesn't contribute to feelings of satiety.

Unlike other macronutrients, alcohol calories are typically consumed in addition to overall energy intake[18,19]. Drinking alcohol lead to increased food consumption, by different mechanisms controlling appetite, including the release of hormones that regulate hunger, intensifying the immediate pleasure of food, and promoting impulsivity and overeating[20], resulting in a potential 30% boost in total energy intake[21–23]

51% of people who drink alcohol admitted having a 'tipping point' (approximately nine units of alcohol), where they begin to make less healthy decisions. The typical extra energy consumed from food and beverages after reaching the "tipping point" is around 4.000 calories on that same evening - double the daily calorie recommendation for an adult woman. Poor food choices on the following day and/or called off scheduled physical exercises, frequently opting for sedentary activities like watching TV or staying in bed are another frequent consequences[20].

The consumption of alcohol in quantities and patterns that lead to health problems, which can include chronic daily drinking and/or binge drinking[13]. In the past few years, alcohol consumption habits have changed, and the phenomenon of drinking too much too fast, termed binge drinking, is growing in Western countries, especially in the UK and northern Europe[24]. The most widely used definition of binge drinking is the consumption of five or more drinks for men and four or more drinks for women in about 2 h on a single occasion or day[25]. Around 20% of adults in Europe and 17% in USA report binge drinking up to once a week often in the context of social events and celebrations as an enjoyable way of socializing and counter-balancing the demands of daily hassles and routines[26]. It is important to note that subjects with SLD who had binge drinking for at least 13 days/year had a significantly increased risk of liver-related hospitalizations and mortality[27] independent of average daily alcohol intake. Although monthly and less-than-monthly binges also displayed heightened risk estimates, the effect became statistically significant for weekly binge drinking[27].

Only in the US, an estimated 80.19 million individuals have SLD. Among them, MetALD affects approximately 21.9–33.05 million people and about 5.33 million have clinically significant fibrosis[28,29]. In comparison, MASLD impacts 44.9–45.93 million people and pure ALD 5.9 million adults[28].

Recent reanalysis of the UK Biobank data using the updated terminology revealed that out of 10.656 patients with a cardiovascular risk factor, 9.509 (89.2%) were now considered to have MASLD, while the remaining 1.147 (10.8%) were categorized as MetALD[30].

Furthermore, currently available data on SLD epidemiology need to be evaluated cautiously given that underlying databases largely did not account for systematic screening for alcohol consumption in MASLD patients. Moreover, a substantial number of patients with NAFLD/MASLD may consume unreported amounts of alcohol[31,32]. Such as, study by Sttockwell et al. clearly indicated that 28.6% of patients thought to have NAFLD were in danger of liver damage caused by alcohol[33].

It has been widely known that surveys on self-reported alcohol consumption (e.g. AUDIT-C or CAGE)[34,35] show lower consumption and typically cover around 40–60% of the recorded alcohol sales data. Nevertheless, self-report techniques are the foundation of almost all research on the negative health impacts of alcohol[33], giving individuals with alcohol addictions face negative social judgment. Therefore, it appears that patients commonly fail to accurately report or underestimate how much alcohol they consume[36].

The Alcoholic Liver Disease/Nonalcoholic Fatty Liver Disease Index (ANI) scoring system, which consider mean corpuscular volume (MCV), aspartate/alanine aminotransferase (AST/ALT) ratio, Body Mass Index (BMI), and male gender is one of the useful tools in detecting excessive alcohol intake. However, it is not reliable for identifying repeated moderate alcohol consumption and is not accurate for patients with advanced liver disease[37].

The indirect alcohol biomarkers, including carbohydrate-deficient transferrin (CDT), glutamyl transpeptidase (GGT), and cholesteryl ester transfer protein (CETP), are also effective in indicating heavy alcohol use[38]. A metabolite of alcohol, ethyl glucuronide (EtG), found in both hair (hEtG) and urine samples (uEtG) shows great accuracy in detecting regular to heavy

alcohol consumption. uEtG is a specific alcohol marker that remains detectable in the body for up to 80 h after ethanol (EtOH) elimination and up to 130 h after consuming large amounts of alcohol. Notably, uEtG levels are not influenced by the presence of cirrhosis or BMI. hEtG is a marker for alcohol intake over a longer period, able to approximately identify drinking habits in the past 3 to 6 months and differentiate between minimal or none, occasional moderate, and excessive alcohol consumption[32,39]. Phosphatidylethanol (PEth) in blood is another highly sensitive (94% to 100%) and specific (100%) alcohol biomarker, which only forms in the presence of EtOH and can detect alcohol use the previous 2–4 weeks[40].

Further research is required to discover biomarkers that are more sensitive and specific for varying levels and patterns of alcohol consumption. Incorporating these biomarkers into clinical practice and research will enhance the precision and depth of data, potentially leading to improved strategies for diagnosing and identifying patients who are at increased risk of liver disease progression because of their alcohol consumption.

Sex-related disparities in prevalence, risks, and mechanisms of SLD have been acknowledged for a long time but are not fully understood. Latest analysis of National Health and Nutrition Examination Survey of the U.S. population (NHANES III (1988–1994, $N = 31.311$)) revealed significantly different prevalence of SLD phenotypes between men and women. MetALD, MASLD, and ALD prevalence in men was 3.2%, 18.5%, and 1.7%, respectively, while the corresponding prevalence in women was 1.2%, 10.3%, and 0.3%[41]. In line, in freshly analysed UK Biobank data the majority of individuals in the MetALD group were males, in comparison the MASLD group had a slightly smaller percentage of males (66% vs. 60%)[30]. NHANES analysis between 2017 and March 2020 (7.711 adults) further confirmed this data[42].

Gender roles and social norms lead to different lifestyle risk factors for men and women. Hence, male tend to engage more unhealthy behaviours, including smoking and alcohol consumption, which are widely regarded as desirable male norms in most parts of the world.

However, MetALD was associated with 83% higher hazard of all-cause mortality in women. The excess mortality risk in females is likely driven by either presence or predominance of excess alcohol intake over the metabolic factors alone. Women are almost twice as likely as men to experience more severe ALD and develop cirrhosis at lower alcohol doses and with shorter drinking periods[41,43] Multiple research studies have indicated different blood alcohol levels between women and men consuming the same quantity of alcohol. This discrepancy could be attributed to differences in gastric alcohol dehydrogenase (ADH) levels, higher body fat percentage in women, or fluctuations in alcohol absorption during the menstrual cycle[44].

Overall, limiting alcohol intake in women with SLD, may be crucial as part of efforts to mitigate mortality risk[41].

The cessation of ovarian function favours dysmetabolism and dyslipidaemia and increases the likelihood of MASLD in the group of postmenopausal women by around 2.4 times[45]. Males aged >50 years, are also at increased risk of progressive fibrosis and the development of cirrhosis and its complications[45]. In general, old age is one of the risk factors for developing SLD, the main factor for their complication and progress to the end stage, as well as limiting factor in specific therapeutic approaches. Therefore, it is crucial to comprehend the potential advantages and disadvantages of various treatment choices in elderly individuals in order to create safe and efficient treatments[46].

Various research indicates that there are disparities in the occurrence and severity of SLD among different racial or ethnic groups, potentially due to variations in lifestyle, diet, metabolic comorbidities, and genetic factors. Representative study analysis of NHANES (2017–2018) revealed that among racial groups, Mexican American demonstrated higher prevalence rates for MetALD. However, the prevalence of disease severity: steatohepatitis, advanced fibrosis, and cirrhosis, was highest among caucasian-adults with MetALD.

Certainly, genetic architecture varies among populations of diverse ethnic origins and accounts for more than half of the inter-ethnic variability in the predisposition to develop SLD. For example, PNPLA3 I148M variant accounts for over 50% of the differences in genetic predisposition for developing SLD across different ethnic groups. Of note, PNPLA3 rs6006460[T] is associated with lower hepatic fat content and common in African Americans but rare in Hispanics and European Americans[47].

Undeniably, the associations between ethnicity and SLD are not only driven by metabolic risk factors and alcohol use but also mediated by social factors as education access and, economic stability, health care access, neighbourhood and community context. Obviously, more research is needed to assess strategies aimed at improving social health determinants, such as availability of alcohol and food quality, in order to address race and ethnic disparities in MetALD[29].

However, it is obvious that results obtained in American and European studies might not be relevant in Chinese, Japanese, and Korean populations, which are genetically different in terms of insulin sensitivity, β-cell function, as well as ability to metabolize alcohol. Approximately 36% of East Asians (560 million) carry an inactivating mutation of the aldehyde dehydrogenase 2 (*ALDH2)* gene. This mutation is strongly associated with high sensitivity to alcohol, Type 2 diabetes mellitus (T2DM), body mass index, and serum lipids in East Asians[48]. The genetic factors make Asians highly susceptible to developing type T2DM, even without being overweight[49]. In fact, the moderate alcohol intake raises the possibility of T2DM, particularly in slender Japanese people[50].

In fact, up to 75% of SLD variability in the population is accounted for by inherited factors. It is likely that understanding of MetALD genetic underpinnings represents great opportunities for personalized medicine and will play a growing role in the future[13,51].

Several lifestyle factors, such as unhealthy diet, tobacco smoking, short sleep duration and lack of physical activity are crucial but modifiable risk factors for SLD. For example, there is a well-known association between alcohol consumption and smoking, important profibrogenic habit. Clinical evidence indicates that cigarette smoking negatively impacts the incidence and severity of SLD, fibrosis progression and HCC development[52]. Moreover, there is a direct effect of tobacco on IR, resulting in higher prevalence of hepatic fibrosis in patients with T2DM. Adiponectin, a secretory adipokine produced by adipocytes and significant in lipid metabolism, may be the mediating factor in this association[53]. The deleterious effect of smoking on the progression of liver fibrosis is particularly pronounced in regular alcohol consumers. There is a clear need to perform both retrospective and prospective large cohort studies to explore this particular synergism in the context of MetALD.

Metald – Diagnosis and prognosis

The relationship between MASLD and alcohol intake has been a topic of debate in recent years. At first, a few research studies indicated that moderate amounts of alcohol could have a protective impact[54–61]. Nevertheless, according to the latest Global Burden of Disease report[62], consuming even one standard drink per day raises the risk of illness and death, particularly in young individuals. In the presence of MetS the excessive alcohol intake has negative effects at 3 drinks per day; in patients without MetS, a similar association is not observed until the consumption of alcohol increases to at least 6 drinks/day for men, 3 drinks/day for woman[27]. The data indicates that there is no amount of alcohol consumption that can be considered safe, and it is currently advised that MASLD patients should abstain from alcohol entirely[63]. Alcohol drinking poses a substantial threat to the advancement of liver diseases in people with MASLD and metabolic syndrome (MetS), ultimately affecting the mortality rate in those patients[64]. Among MASLD patients with excessive alcohol consumption, the primary driver of steatosis is likely to be metabolic dysfunction and not excessive alcohol consumption[65].

UK Biobank analysis of baseline serum markers has revealed higher levels of ALT and AST in MetALD compared to the MASLD group. Moreover, consistently with other studies[66,67] the most altered liver-related parameter was γ-glutamyltransferase (GGT)[30]. Earlier research has shown that GGT plays a role in glutathione metabolism and safeguards cells from damage caused by free radicals and peroxidase. Upon sensing oxidative

stress, GGT levels rise significantly to boost glutathione synthesis. Hence, an abundance of alcohol consumption could result in heightened GGT levels[68].

The ratio in between AST and ALT, also known as De Ritis ratio (DRR), has been used as a liver function test to differentiate the causes of liver damage or hepatoxicity, with a ratio of 2:1 or greater being suggestive of alcoholic liver disease, particularly in the presence of elevated GGT[69]. This ratio is a dynamic biochemical parameter and tends to increase due to hepatic cell destruction and the release of AST from mitochondria[70]. Elevated transaminases and GGT are significantly associated with mortality from liver disease. Importantly, the DRR was likewise associated with all-cause, cardiovascular disease (CVD), and cancer mortality[71]. Further studies may validate these findings in MetALD population.

Notably, non-invasive test called FIB-4, which combines standard biochemical values (platelets, ALT, AST) and age, exhibited a high performance and demonstrate reasonable sensitivity for the initial screening of advanced hepatic fibrosis in MetALD[72].

The cohort study with 12.656 participants clearly showed that MASLD and excessive alcohol are simultaneous but independent predictors for mortality. MASLD was associated with increased mortality risk in participants with and without excessive alcohol consumption. However, the patients with both MASLD and excessive alcohol consumption expressed the highest mortality risk[65]. The cohort study analysis by Younossi et al.[27] and Mengqi Li[73] confirmed that alcohol consumption increase mortality in participants with SLD and MetS and that patients with MetALD have a poorer prognosis. Subjects with fatty liver disease who had binge drinking for at least 13 days/year had a significantly increased risk of mortality[27].

Very recent study enrolled in Spain and U.S. showed that moderate alcohol consumption has a supra-additive effect with metabolic risk factors, exponentially increasing the risk of liver fibrosis[74]. These findings are in line with studies enrolled with 765 Japanese[75] or 300 Sweden patients[40] and reporting a higher occurrence and cirrhosis-related complications of fibrosis in MASLD individuals, with moderate alcohol consumption. Furthermore, epidemiological studies using a large cohorts of patients in Northern Italy[67], France[76], Scotland[77], China[78] and South Korea[79] clearly showed that that obese alcoholics have 2–3 times higher risk of developing steatohepatitis and dramatically increased progression to fibrosis or cirrhosis. NAFLD patients with T2DM consuming moderate amounts of alcohol seem to be at the highest risk for advanced fibrosis[80]. Hence, obese individuals consuming 15 or more drinks per week have an adjusted relative rate of liver-related death of 18.9 compared to 3.16 in their lean counterparts[77].

The risk of having MetS is higher with substantial or excessive alcohol use: a mild alcohol intake with 100–300 kcal/day can contribute directly to weight gain and obesity, irrespective of the type of alcohol consumed[81].

The impact of alcohol consumption is associated not only with incidence of steatosis, fibrosis progression, and mortality but also with less resolution of steatohepatitis and steatosis compared to consistent non-drinkers on adjusted analysis of the longitudinal cohort of MASLD patient. The switching from a moderate drinker to a non-drinker lead to histologic improvement and weight loss[82].

All SLD subtypes are at a higher risk of developing primary liver cancer (PLCa), including hepatocellular carcinoma (HCC)[83–86]. Hence, the combination of obesity and T2DM are potential risks for HCC in individuals with ALD, while high alcohol intake raises the likelihood of HCC in those with MetS[64]. Several studies described that a mild drinking habit is associated with an increased risk of carcinogenesis in MASLD-associated patients[87,88]. The study of Kawamura et al. showed that HCC incidence after long-term follow-up in patients with MASLD was 0.28%. In contrast, the incidence of HCC related to high-intermediate alcohol intake and SLD was 0.63%, with an annual rate of 0.16%[89]. The participants of Korean nationwide study with MetALD showed approximately 87% higher risk to develop PLCa compared to those without SLD, while MASLD patients had a 65% increased risk[85]. In addition, the risk of HCC was lower in the group of patients with MASLD and MetALD taking antidyslipidemic drugs, which might be explained by a substantial preventive effect of statins against HCC[90]. In line, the risk of HCC in obese patients who consume alcohol at least 4 days per week increased by 7-fold in a prospective population-based study with 23.712 Taiwanese patients who were followed for 11.6 years[91].

However, alcohol consumption not only increases liver-related morbidity and mortality but affects numerous extrahepatic organs. A recent national study in South Korea with 351.068 participants showed that people with SLD faced a greater chance of developing cardiovascular disease (CVD). Importantly, the risk of CVD increasing from no SLD to MASLD and then to MetALD, showing that alcohol consumption, when combined with cardiometabolic risk factors, plays a significant role[92]. A key mechanism contributing to cardiometabolic comorbidities like hypertension, dyslipidaemia, T2DM, and obesity is endothelial dysfunction caused by decreased nitric oxide production, increased inflammation and oxidative stress[93,94]. Therefore, changing the drinking habits or recommending abstinence in addition to reducing the cardiometabolic load could be a helpful treatment choice for individuals with MetALD.

Metald - Add insult to injury

MASLD and ALD are two distinct pathological entities but have many clinical similarities and share multiple complex pathogenic mechanisms. In both diseases the disturbed lipid metabolism in hepatocyte leads to intracellular build-up of potentially toxic bioactive lipid species causing endoplasmic reticulum (ER) stress, mitochondrial dysfunction and cellular death, which in turn triggers the innate immune response and activation of hepatic stellate cells (HSCs), resulting in inflammation and increased collagen production and deposition. Hence, this general sequence varies between MASLD and ALD and additionally is influenced by various genetic and epigenetic factors[81].

Current evidence suggests that in case of MetALD the overlapping features of alcohol and MetS leading to liver damage are either additive or synergistic[64]. However, it would be very simplistic to insinuate that MetALD is just a simple sum of ALD plus MASLD. For example, obesity, insulin resistance (IR), MetS has significant impact on alcohol metabolism and clearance[95] pathways, increasing toxicity and causing a profound aggravation of liver damage.

Alcohol metabolism is a well-characterized biological process primarily controlled by the alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) families. Over 90% of consumed alcohol is first oxidized to aldehyde by ADH, followed by ALDH-mediated aldehyde metabolism to acetate[96]. The disbalance in the metabolizing enzymes after alcohol consumption increases the toxic properties of its major metabolite - acetaldehyde[97]. Notably decrease of ADH and ALDH activity in MASLD patients can decrease alcohol elimination, impair acetaldehyde detoxification and increase sensitivity to alcohol toxicity[98].

Several studies reported that IR, insulin-dependent signalling cascades[99] and tumour necrosis factor alpha (TNFα) are the critical component in MASLD progression, which can modulate alcohol metabolism in human and mouse models and modify the activity of ADH.

In the liver of the ob/ob mice demonstrating marked signs of hepatic IR, the activity of ADH was significantly lower than in lean controls[99]. In line with these findings, in rats the activity of ADH was significantly reduced in diabetic models as well as in animals fed by high-carbohydrate, fat-free diet[100].

It is worth to mention that ADHs might also play a role in additional molecular pathways significant for SLD development. For example, ADHs are involved in the biosynthesis of retinoic acid (RA), an active metabolite of retinol[101]. RA has a broad range of biological effects, including the synthesis of retinoids, phospholipids, and unsaturated fatty acids. It also has a direct impact on several biological processes, such as short-chain fatty acid (SCFA) oxidation, and triglyceride (TG) degradation[102–104]. Long-term dietary supplementation with RA robustly alleviated hepatic steatosis in high-fat diet (HFD)–fed C57BL/6 mice. In human circulating RA concentrations is lower in patients with MASLD. Thus, RA exerts extensive beneficial effects in maintaining lipid homeostasis in the liver[105]. Prior research has indicated that alcohol may disrupt RA balance by inhibiting ADH-mediated oxidation of retinol to retinal, a key step in RA biosynthesis[106].

The decreased ALDH activity was reported in MASLD patients and may indicate an impaired acetaldehyde detoxification and increase their sensitivity to alcohol associated toxicity[98]. Aldehyde dehydrogenase 2 (ALDH2) expression negatively correlates with obesity in mice[107], and patients with active ALDH2 genotype are more obese than those with a low active ALDH2 genotype[108].

Hence, mitochondrial ALDH2, is a critical enzyme not only for oxidation of acetaldehyde to acetic acid in alcohol metabolism, but also for 4-Hydroxynonenal (4-HNE) metabolism[109,110]. Elevated formation of intracellular 4-HNE-protein adducts in adipocytes/adipose tissues contributes to obesity-related lipolytic activation[111] and positively linked to obesity.

In the elegant study, Vilar-Gomez showed that ADH1B*2 allele of the alcohol dehydrogenase 1B gene is associated with higher alcohol metabolism and might affect the relationship between moderate alcohol consumption and severity of MASLD. The individuals with ADH1B*2 have significantly decreased risk of several histologic features of MASLD, including hepatocyte ballooning, lobular inflammation, steatohepatitis, and fibrosis activity score[112]. As ADH1B*2 allele leads to faster alcohol metabolism, it potentially causes less effective alcohol energy utilization and results in lower weight gain compared to alcohol dehydrogenase 1B (Class I), beta polypeptide allele 1 (ADH1B*1) carriers[113].

A minor pathway for alcohol metabolism (<10% under normal conditions) is comprised of cytochrome P450 2E1 (CYP2E1) and catalase[96]. Liver overexpressing transgenic CYP2E1 mice demonstrated increased plasma lipid levels, decreased glucose tolerance, and increased liver steatosis[114]. Consistently, constitutive CYP2E1KO mice have reduced plasma lipid levels, increased glucose tolerance, and are protected against HFD-induced IR with increased energy expenditure[115].

IR can enhance the levels of CYP2E1 expression and activity via the elevated production of ketone bodies from persistent mitochondrial fatty acid oxidation. Ketone bodies stabilize CYP2E1 and halt its degradation. The rise in CYP2E1 and enhanced IR appear to mutually reinforce each other, leading to a cycle that may eventually make steatosis progress to steatohepatitis as oxidant stress increases[116].

The liver is generally considered to be responsible for more than 90% of alcohol oxidation. However, white adipose tissue (WAT) also expresses alcohol oxidizing enzymes (ADH, catalase, and ALDH2). This finding led to the question of whether WAT could play a role in total body alcohol metabolism especially in obese individuals (even if WAT has 1/10th the ADH activity of liver, obese individuals may have 50 times more WAT than liver), although this could vary depending on genetic and/or environmental factors[117].

Of note, ALDH2 is also expressed in astrocytes in specific brain regions. Important, but previously under-recognized astrocytic ALDH2 mediates behavioral effects associated with alcohol intoxication and impairment of balance and coordination skills.[118]

The altered pathways of alcohol metabolism in the liver of obese and diabetic patients are the result of impaired insulin signalling along with overproduction of endogenous alcohol by intestinal bacteria. Several studies have emphasized that ethanol produced by microbes in the gut may play a role in the development of MASLD[119]. Indeed, patients and mice with manifested MASLD have markedly higher breath and blood alcohol, and also acetaldehyde levels, even in the absence of alcohol consumption[120]. Both gram-negative and gram-positive bacteria have the ability to produce alcohol in high concentrations. Bacterial species belonging to the phylum Proteobacteria, lactic acid bacteria and *Klebsiella pneumoniae*[121] have been associated with fasting alcohol levels in MASLD. The impact of these lineages can differ based on ethnicity, genetics, and other demographic factors[122]. Additionally, increased blood alcohol levels in patients with MASLD correlate with markers of IR[120].

Indeed, the intestinal microbiome is known to play an important role in the progression of SLD. Though many studies investigate intestinal dysbiosis in ALD and MASLD separately[123,124] only few ones specifically focus on the effects of modest alcohol intake on the microbiomes of MetALD patients. Alterations in the abundance and composition of the intestinal microbiota was revealed in MASLD patients with moderated alcohol consumption. A significant positive correlation was seen between low-level daily alcohol consumption and the relative abundance of *Bacteroidales*, whereas a negative correlation was observed with dehydroxylating *Lachnospiraceae* leading to reduced production of secondary BA[125]. Another study[126] revealed the abundance of *Bacteroidaceae*, *Bifidobacteroidaceae*, *Streptococcaceae*, and *Ruminococcaceae* in a small group of NASH patients with moderate alcohol intake. Interestingly, *Ruminocaccaceae* family, have been associated with the organic metabolite Trimethylamine N-oxide (TMAO) levels, playing an important role in the development of atherosclerosis and increased cardiovascular risk[127],while *Bifidobacteriaceae* or *Streptococcaceae* influence on glucose and fat metabolism[126].

A recent study by the group of Schnabl[128] on viromes, showed that any alcohol consumption is also associated with changes in the intestinal viral composition of MASLD patients. Hence, the viral diversity of the alcohol-consuming MASLD patients was similar to the ALD group and significantly higher than the non-alcohol-consuming MASLD. Further, alcohol use in MASLD patient was associated with increased intestinal abundance of *Lactococcus* phage which have been previously linked to the more progressed liver disease[129].

Rosetta stone: metald animal models

Animal model that faithfully reproduces all the extrahepatic and intrahepatic features of MetALD would help to understand the synergistic effect of alcohol and metabolic factors. Various hybrid models[130–139] have been proposed to replicate MetALD or MASLD coexistence with alcohol consumption (Table 1). Still, some of these models possess certain drawbacks and do not fully replicate all the physiological, metabolic, histological and clinic characteristics of human steatohepatitis, including hepatic inflammation and advanced fibrosis. This is primarily due to the inherent aversion mice have towards alcohol, resulting on much less alcohol consumption when it is provided for example in their drinking water. Furthermore, rodents do not easily develop addictive behaviour, naturally decrease alcohol consumption as acetaldehyde levels rise, metabolize alcohol quickly, have a high basal metabolic rate and demonstrate certain differences in the innate immune system[140]. These factors make it difficult for rodents to reach and sustain high blood alcohol levels, which in turn explains why they do not experience significant liver damage[141].

When analysing the feeding parameters in each of the models, differences arise. These parameters include animal species and strain, nutritional status, age and gender, as well as the use of appropriate control groups. The circadian rhythm, together with level of alcohol intake, its administration pattern and its duration also present significant variances[142].

The lack of homogeneity and consensus in the scientific community regarding the application of these conditions presents itself as a limiting factor when comparing the different models but can also be considered as an advantage in addressing the disease severity in its different stages, with plenty of tools to mimic the pathophysiology of MetALD.

Summary and new horizons

In 2023 Delphi consensus introduced a separate SLD subcategory, termed MetALD in which metabolic and alcohol-related risk factors coexist[2]. The main reason for this distinction was the harmful impact and negative consequences of drinking alcohol on the prognosis for SLD patients. Importantly, MetALD should not be seen neither as ALD nor as MASLD. Hence, the quick evolution of terminology might lead to difficulties such as confusion and incorrect categorization of patients. Hence, policymakers should ideally support the renaming process. A more rigorous discussions and active involvement of medical professionals would be essential and the translatability of findings across preclinical and clinical research should be also considered.

Our review draws attention to the growing prevalence of MetALD in the world. Moreover, a significant percentage of MetALD patients are at risk for advanced fibrosis, cirrhosis, HCC and CVD. Efforts should focus on

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Table 1 | Animal models proposed to replicate MetALD or MASLD+alcohol consumption

Type of induction	Species and strain *	Induction time	Steatosis	Inflammation	Fibrosis	HCC	Advantages and important characteristics	Disadvantages	Ref.
HFD + 5% EtOH in drinking water	♀ Balb/c	6 week	Yes	Very mild	Yes	No	Easy to set up. Short-term model. Significantly elevated endotoxin levels in the portal circulation, increased TLR4 expression.	No signs of advanced steatohepatitis.	130
Solid WD (2 weeks) followed by implantation of the intragastric catheter (27 g EtOH/kg body weight/day + liquid HFD) 8 week + bonus dose 4-5 g EtOH/kg body weight/week	♂ C57BL/6	10 week	Yes	MNC infiltration	Yes	No	Important clinical features of ALD, including balloon cell degeneration and necrotic hepatocytes surrounded by PMN infiltrates, splenomegaly, hypoalbuminemia, bilirubinemia.	Heterogeneous responses to the treatment. No data about MetS. Not a physiological model, requiring skilled surgical implantation and extensive animal monitoring. Can be classified as severe procedure, thus have potential. Difficulties with local ethics committees.	131
HFD + EtOH gastric gavage twice a week (2 g EtOH/kg body weight as a 30% solution in saline)	♂ C57BL/6	12 week	Yes	Yes (F4/80+ Kupffer cells, CD45 +, CD68+ infiltration)	Yes (histological and molecular)	No	Easy to establish in short term. Very relevant to the real-life setting. Increased body weight, hyperlipidaemia and hyperinsulinaemia. Potentially can be extended to produce more severe fibrosis by either increasing dose of alcohol or duration of treatment.	Inappropriate technique during the oral gavage can be cause of mortality.	132
WD + EtOH in drinking water (20% for 4 days and 10% for 3 days per week)	♂/♀ C57BL/6 J	16 week	Yes	Mild	Yes (pericellular fibrosis)	No	Easy to perform model. It reproduces a very slow and largely asymptomatic disease progression. Demonstrates significant similarly to human chronic ALD. It can be applied equally to both males and females and preserves gender differences in the disease phenotypes as seen in humans.	Reproduces a limited spectrum of human MetALD features due to the very mild gain of weight and the absence of MetS.	133
DUAL diet model (WD + 10% EtOH in sweetened drinking water)	♀ and ♂ C57BL/6 J	23 week	Yes	Yes	Yes	Yes (52 week)	Physiological, easy, affordable, highly reproducible diet with low mortality characterized by obesity, glucose intolerance, liver damage, prominent steatohepatitis and fibrosis, as well as inflammation and fibrosis in white adipose tissue.	Lengthy periods of feeding mice, demanding a significant amount of labor.	134
EtOH binge one single dose of ethanol (5 g/kg body weight as a 53% v/v solution in water) via oral gavage	♂ ob/ob (B6/JGpt-Lepem1C-d25/Gpt)	10 week 9 h after gavage	Yes	Mild neutrophil infiltration in the liver	No	No	Simplicity, low inter-individual heterogeneity.	The etiology of obesity in ob/ob mice can be incompatible with MetALD. Not really a chronical model.	135
WD + 5% EtOH in drinking water + weekly EtOH gavage (2.5 g EtOH/kg body weight)	♂ C57BL/6 J	12 week	Yes	No	No (only increasing expression of pro-fibrotic genes)	No	Experimental mouse model of early MetALD. Impairs glucose intolerance.	Recapitulates histologic steatosis without histologic inflammation or fibrosis.	136
WASH-diet model (liquid WD with 4.5% EtOH (vol/vol))	♂ C57BL/6	7 week	Yes	Upregulation of inflammatory factors IL6 and TGFB	Yes	No	Simple model. Mice display high adiposity, elevated serum cholesterol, TG and markers of liver injury.	Does not recapitulate histological inflammation. Liquid diet requires daily changes and significant amount of labor.	137
MetALD diet (high fat-cholesterol-sugar diet) + 10% EtOH in drinking water + 5 g/kg body weight EtOH gavage weekly	♂ C57BL/6	3 months	Yes	Yes	Yes	No	Mimics the features of MetALD and severe alcohol-associated hepatitis. Hepatic phenotype show molecular signatures of steatosis, inflammation, fibrosis, impaired liver synthetic function, and regeneration.	Survival rate is 85%. Mild MetS	138,139

increasing awareness of the burden of MetALD in the population and mitigate the modifiable risk factors.

MASLD, ALD and new MetALD have many similarities in both pathophysiological and clinical aspects. Even liver histology, considered the gold standard for diagnosis, is unable to accurately differentiate between SLD subcategories. Large, randomized control trials are urgently needed to discover specific biomarkers for early and accurate detection of MetALD to further guide diagnosis and treatment[64]. Hence, the lack of randomized clinical trials, can possibly be explained by preconceived notion that patients with alcohol consumptions are less obedient and more difficult to maintain.

Another serious problem for SLD patients is the underreporting of alcohol consumption. It should also be mentioned in this context that possible positive impacts of certain drugs (for example semaglutide[143]) observed in MASLD trials can be linked to a decrease in alcohol intake[12]. Future drug trials on SLD should include participants with MetALD and assess the efficacy of therapies originally developed for MASLD patients.

Animal models remain the most comprehensive approach to study the pathophysiology of liver diseases and to develop new medication. However, given the complexity of MetALD it is not easy to mimic the disease in vivo and to translate findings from animals to humans. We expect that in the near future complex in vitro models (such as liver-on-a-chip platforms or three-dimensional (3D) models), will enhance our understanding of mechanisms, reproduce the inter-individual variability and capture multiple organs interactions involved in the systematic pathogenesis of MetALD.

Additionally, educational programs and lifestyle interventions are essential to acknowledge the prevalence of this new clinical entity. We suggest more public health campaigns and communications addressing the links between alcohol, obesity and SLD. Existing alcohol campaigns only briefly touch the effects of alcohol calories on weight gain and do not discuss how drinking can affect food consumption and physical activity. This must be included in alcohol-related public health guidance[144]. Moreover, instead of the management of end stage complications, the focus should be shifted towards prevention, proactive case finding with early identification of MetALD, early diagnosis, and early treatment[20].

Data availability

No datasets were generated or analysed during the current study.

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O.E.-V., and H.L.L. performed literature search, writing, revision of the manuscript. F.J.C. helped with the manuscript draft. Y.A.N. provided fundamental insight and conception of the work, drafted the paper. All authors critically reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests.

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