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From NAFLD to MAFLD and MASLD: a tale of alcohol, stigma and metabolic dysfunction

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Abstract

Liver steatosis is a frequent finding in clinical practice and it is estimated to affect 30% of the general adult population worldwide. It became one of the leading causes of end-stage liver disease and hepatocellular carcinoma. From its first description, a diagnosis of nonalcoholic fatty liver disease (NAFLD) required the exclusion of excessive alcohol consumption and concomitant chronic liver diseases of different origins, making it a diagnosis of exclusion. In recent years, the need to stress the strict association between liver steatosis and metabolic dysfunction (i.e., insulin resistance, overweight/obesity, type 2 diabetes, and metabolic syndrome), as well as the desire to define a condition in a positive rather than negative way, led to new definitions and new diagnostic criteria. Metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed by Eslam *et al.* in 2020. More recently, a Delphi consensus endorsed by several international hepatologic societies proposed a new terminology [metabolic dysfunction-associated steatotic liver disease (MASLD)] and a new set of diagnostic criteria. The MAFLD and MASLD definitions have a good degree of concordance. They mainly differ in the number of metabolic derangements needed to define "metabolic dysfunction" in normal-weight individuals and in alcohol consumption. Indeed, while MAFLD does not exclude patients with significant alcohol consumption, the recent Delphi consensus included the metabolic dysfunction and alcohol-related liver disease (MetALD) disease entity, a condition in which steatosis, metabolic dysfunction, and moderate alcohol intake coexist. In the present narrative review, we underline the strengths and possible limitations of each definition and summarize available evidence from epidemiologic studies evaluating the clinical usefulness of each set of diagnostic criteria.

Keywords: Nonalcoholic fatty liver disease (NAFLD), metabolic dysfunction-associated fatty liver disease (MAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-related liver disease(MetALD), insulin resistance, nomenclature

HISTORICAL AND EPIDEMIOLOGIC ASPECTS

Descriptions of liver steatosis by pathologists date back to the first half of the nineteenth century[1,2]. Several Authors identified associations between liver fat and alcohol consumption, visceral adiposity and conditions such as tuberculosis[3,4]. Decades later, in the mid-twentieth century, sporadic observations started to suggest a possible link between liver fat and the development of more advanced forms of liver disease, including cirrhosis[5]. Nonetheless, this association remained controversial for many years, with many authors skeptical of this theory[6,7].

The first description of liver steatosis with inflammation and a thorough description of the associated histologic changes were made in 1980 by Ludwig *et al.*[8]. The Authors studied a sample of middle-aged patients with overweight obesity and a high prevalence of type 2 diabetes who consumed little or no alcohol. They showed that the histologic changes within their livers were undistinguishable from those typically associated with elevated alcohol consumption (including lobular inflammation, Mallory bodies, and various degrees of liver fibrosis). Therefore, they named this condition "nonalcoholic steatohepatitis (NASH)". In the following years, the term nonalcoholic fatty liver disease (NAFLD) was introduced as an umbrella term including patients with liver steatosis not related to alcohol and all stages of histologic changes in terms of inflammation and fibrosis[9]. It became clear that this was not always a benign condition and that it could lead to liver cirrhosis and related complications[10].

In the last few decades, the interest in this condition increased dramatically and several pieces of the puzzle were put into place. On the one hand, many studies showed that insulin resistance was a major contributor to the development and progression of NAFLD[11], which was strictly associated with features of the metabolic syndrome including diabetes[12], visceral adiposity[13], hypertension[14], and dyslipidemia[15]. Indeed, paralleling the increasing rates of obesity and type 2 diabetes, NAFLD became by far the most common chronic liver condition worldwide, affecting 30% of adults[16-19] and 10%-15% of children/adolescents[20,21], with significant differences across continents. On the other, specific histologic scoring systems were introduced to evaluate the grade and stage of the disease and assist in the standardization of histology-based studies[22]. It became evident that the degree of liver fibrosis was the major predictor of the future development of liver-related events and hepatocellular carcinoma, as it occurs in several chronic liver conditions[23-25]. Nonetheless, it should be mentioned that approximately 30% of cases of hepatocellular carcinoma diagnosed in patients with NAFLD/metabolic dysfunction-associated steatotic liver disease (MASLD) develop on a non-cirrhotic liver, making it extremely challenging to detect in the early stages[26,27].

Today, NAFLD is viewed as a heterogeneous condition with a complex pathophysiology [Figure 1]. Noxious stimuli are from different origins. Apart from lifestyle factors related to excessive caloric intake, reduced energy expenditure and the relative increase in visceral and ectopic fat deposition[28], ethnicity and genetic factors can influence its development and progression[29]. The most robust associations have been made with variants in the *PNPLA3*[30], *TM6SF2*[31], and *MBOAT7* genes[32,33]. It is believed that genetic factors, alongside differences in lifestyle, diet, metabolic comorbidity profile and socioeconomic status, account for a large proportion of the differences in prevalence across different ethnic groups[34]. Indeed, several studies have shown a higher prevalence of NAFLD/MASLD among Hispanic individuals and a lower prevalence among African individuals, compared with non-Hispanic whites[35]. Moreover, environmental factors such as pollutants and endocrine disruptors are believed to play a significant role as well[36-38].

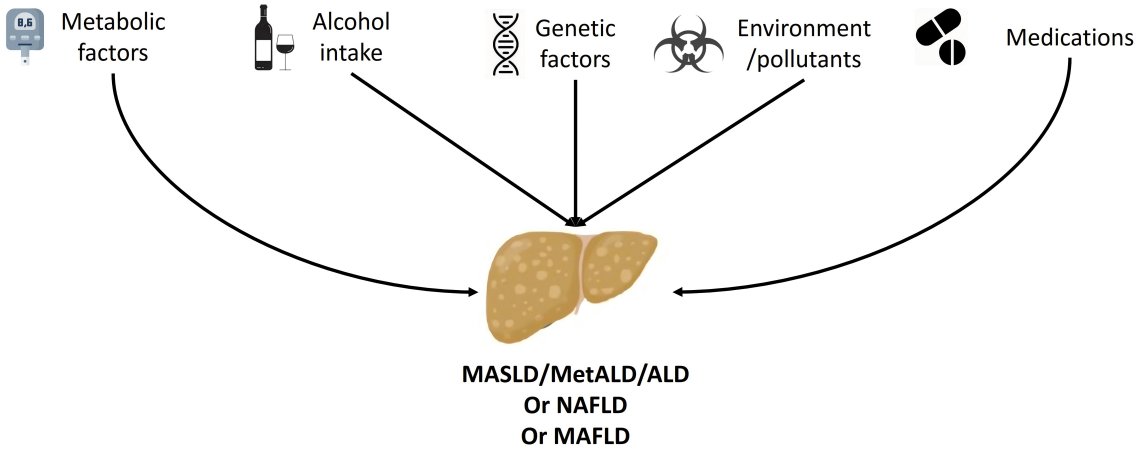

Figure 1. Factors contributing to the development of liver steatosis. MASLD: Metabolic dysfunction-associated steatotic liver disease; NAFLD: nonalcoholic fatty liver disease; MAFLD: metabolic dysfunction-associated fatty liver disease; MetALD: metabolic dysfunction and alcohol-related liver disease; ALD: alcoholic liver disease.

Nonetheless, several areas of uncertainty remain in our understanding of this condition. These span from a more comprehensive understanding of its pathophysiology, to unlocking the key drivers of inflammation and fibrosis, identifying accurate and available diagnostic tests, the cost-effectiveness of screening strategies, the molecular mechanisms linking NAFLD/MASLD to extrahepatic complications, and whether treatment can reduce liver-related events[39].

Finally, in terms of natural history, cohort studies have shown that patients with NAFLD are at increased risk of developing diabetes[40], chronic kidney disease[41,42], extrahepatic cancers[43] and cardiovascular disease (CVD)[44], and heart failure [Figure 2][45]. Indeed, CVD (together with cancer) represents the most common cause of death in these patients, while liver-related mortality becomes a significant concern once inflammation and fibrosis are present[46,47].

ALCOHOL CONSUMPTION AND PERCEIVED STIGMA

Following the advent of highly effective treatments for hepatitis C and widespread hepatitis B vaccination, alcohol-related liver disease (ALD) and NAFLD became the most common disease entities leading to cirrhosis and liver transplantation in developed countries[48]. Indeed, alcohol use and obesity have been identified as the major forces driving liver disease in the general population[49].

While in some instances, it is clear that one factor (metabolic dysfunction or alcohol) is the predominant noxious stimulus leading to liver disease progression, these two conditions frequently overlap[50]. Furthermore, their negative impact on liver health is synergistic rather than additive and if combined with genetic polymorphisms (i.e., variants in the *PNPLA3* gene), they can increase the risk of liver cirrhosis, hepatocellular carcinoma, and death by more than eightfold[51]. Alcohol consumption is highly prevalent worldwide. According to the World Health Organization's global status report on alcohol and health, 43% of people worldwide consumed alcohol in 2018, with the average consumption per capita per year reaching 6.4 liters in 2016[52]. Spirits were the most commonly consumed alcoholic beverages, followed by beer and wine. Moreover, 5.1% of the general population met the definition of alcohol use disorder according to the Diagnostic and Statistical Manual of Mental Disorders. When interpreting these results, it is important to note that the data are only as reliable as the original source data. For instance, consumer surveys assessing

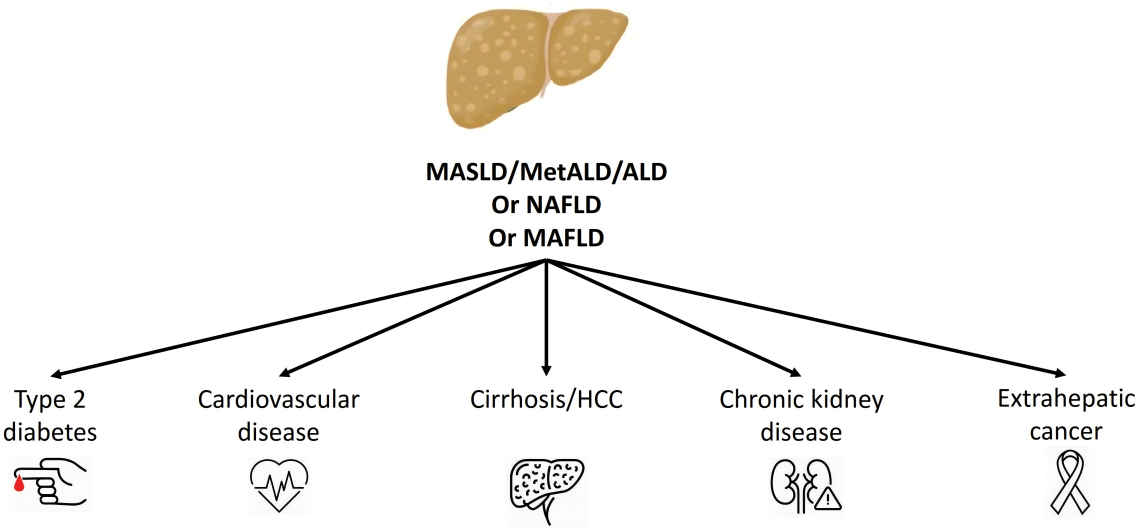

Figure 2. Intra- and extrahepatic complications of liver steatosis.MASLD: Metabolic dysfunction-associated steatotic liver disease; NAFLD: nonalcoholic fatty liver disease; MAFLD: metabolic dysfunction-associated fatty liver disease; MetALD: metabolic dysfunction and alcohol-related liver disease; ALD: alcoholic liver disease; HCC: hepatocellular carcinoma.

people's self-reported alcohol consumption usually show overall consumption figures, which are much lower, quite often around 40%-60% compared with supply-based estimates (i.e., data on the production and trade of alcohol). Moreover, the quality of the data might differ from country to country.

A relevant question in terms of distinguishing between NAFLD and ALD is whether there is a safe threshold for alcohol consumption in the setting of liver steatosis. On this aspect, recent studies seem to identify a linear relationship between alcohol use and health outcomes, with no specific threshold, especially in young individuals[53,54]. Nonetheless, defining a safe threshold of alcohol is complex because it is influenced by multiple factors, including age, sex, diet, drinking behavior, and other disease conditions. This has been one of the criticisms of the NAFLD definition, as it allows quantities of alcohol intake that are not considered safe anymore.

It is, therefore, of great importance to obtain a reliable estimate of patients' alcohol consumption. This is frequently difficult to achieve in clinical practice, as we currently lack objective and reliable biomarkers for widespread use[55,56]. Generally, the use of the AUDIT questionnaire is recommended as a rapid screening tool[57], even though it was developed to detect harmful use of alcohol rather than moderate alcohol use. Nonetheless, relying only on patient reports can result in unrealistic estimates due to perceived stigma and recall bias. This aspect was recently shown in an elegant study performed in Austria[58]. The Authors included a total of 184 patients. They performed an AUDIT questionnaire on all patients and measured ethyl glucuronide (a metabolite of ethanol) in hair (hEtG) and urine (uEtG). They found that 28.6% of patients previously classified as having NAFLD were at moderate to high risk of alcohol-related liver damage[59]. These results challenge clinical practice and dichotomous definitions, highlighting the need to develop reliable markers of alcohol consumption that can be routinely used in the context of liver steatosis.

One of the major factors leading to under-reporting alcohol consumption is social stigma, a problem that affects many chronic metabolic and psychiatric disorders[60,61]. This aspect has been identified as one of the reasons to move from the NAFLD definition (which has the term "alcoholic", even though with a negative

particle before it) to a positive definition related to metabolic dysfunction in both the metabolic dysfunction-associated fatty liver disease (MAFLD) and MASLD definitions. While stigma on alcohol consumption is frequently perceived, fewer data are available on whether the word "non-alcoholic" contained in NAFLD/NASH may also carry this unpleasant burden.

The potential stigma related to the term NAFLD has been recently investigated in a global survey completed by both patients and healthcare providers[62]. The survey showed that the degree of perceived stigma was highly heterogeneous across countries (it was generally higher in the United States) and differed significantly between patients and physicians. Overall, patients reported more commonly stigmatization related to overweight-obesity (26%) than related to NAFLD (8%). They generally felt similarly comfortable with the terms NAFLD and MAFLD. Among practitioners, the word "nonalcoholic" was considered stigmatizing by 34% of respondents, while the word "fatty" by 38%. These discrepancies and geographical differences led some Authors to propose continuing the use of both the NAFLD and MAFLD/MASLD terminology within the scientific community[63].

COMPARING THE DEFINITIONS OF NAFLD, MAFLD AND MASLD

Diagnostic criteria for the three considered definitions are shown in Figure 3. As described before, international guidelines recommended diagnosing NAFLD by demonstrating excessive fat content in the liver (steatosis in ≥ 5% of hepatocytes as evaluated through liver biopsy or histology). Moreover, they recommended excluding other causes of steatosis (such as specific medications and genetic disorders), co-existence of other forms of chronic liver disease (such as chronic viral hepatitis, autoimmune disease, hemochromatosis, and Wilson's disease, among others) and the concomitant use of significant amounts of alcohol[64-68]. Agreement on the exact threshold for defining excessive alcohol consumption is not universal; it has been defined as ≥ 30 g/day in men and ≥ 20 g/day in women, or 2 standard drinks per day for men and 1 standard drink per day for women.

In contrast, to diagnose MAFLD, evidence of liver steatosis may come from histology, imaging techniques, or even serum-based biomarkers [such as the fatty liver index (FLI)]. Furthermore, metabolic dysfunction needs to be present[69]. It is defined as the presence of overweight or obesity (with BMI thresholds differing according to ethnicity), type 2 diabetes (T2D) or, in normal-weight individuals, as the presence of at least two of the following features: increased waist circumference, elevated blood pressure, elevated plasma triglycerides, low plasma High-density lipoprotein (HDL-cholesterol), pre-diabetes, an elevated homeostatic model assessment of insulin resistance (HOMA-IR), an elevated high-sensitivity C-reactive protein. Importantly, exclusion of other forms of chronic liver disease and significant alcohol consumption is not needed to perform the diagnosis, leading to the possibility of diagnosing patients with more than one chronic liver condition.

The recent Delphi consensus, in an effort to provide a more transparent, universal, and systematic process, redefined the whole landscape of liver steatosis. When steatosis is present (mainly detected through imaging or histology), a diagnosis of steatotic liver disease (SLD) can be made[70]. Within SLD, MASLD is characterized by the absence of significant alcohol consumption (using 30/20 g/day in men and women, respectively, as a threshold), other specific etiologies (e.g., drug-induced liver injury or monogenic forms), and evidence of at least one of the following cardio-metabolic criteria: elevated BMI or waist circumference, pre-diabetes or T2D, elevated blood pressure, elevated triglycerides, and low HDL-cholesterol. In the case of steatosis, metabolic dysfunction, and a higher alcohol intake (20-50 and 30-60 g/day in women and men, respectively), a diagnosis of "MASLD and increased alcohol intake (MetALD)" can be made. For even higher alcohol consumption, a diagnosis of ALD is recommended. Finally, in the case of SLD without

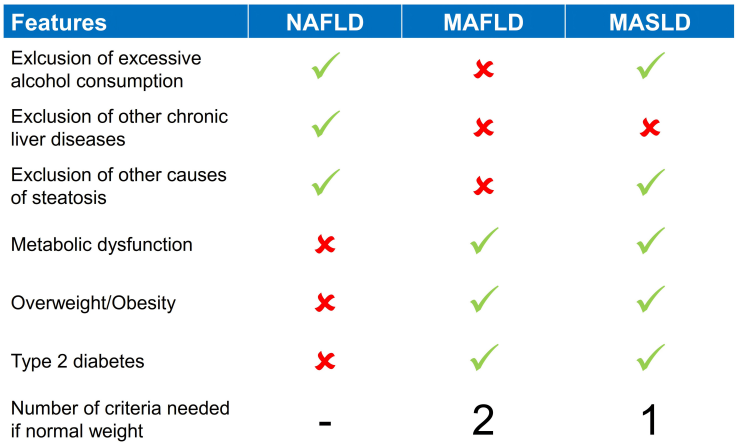

Figure 3. Comparison between the NAFLD, MAFLD and MASLD definitions. NAFLD: Nonalcoholic fatty liver disease; MAFLD: metabolic dysfunction-associated fatty liver disease; MASLD: Metabolic dysfunction-associated steatotic liver disease.

metabolic dysfunction or a specific etiology, cryptogenic SLD is diagnosed.

Several studies have made comparisons between these disease entities. Based on the definitions themselves, it is possible to estimate the features of patients in the non-overlapping groups. Patients with MAFLD but without NAFLD are characterized by the presence of coexisting forms of liver disease or significant alcohol consumption (features that prevent a diagnosis of NAFLD). It is, therefore, conceivable that these patients are at higher risk of liver-related events due to multiple etiologies simultaneously leading to hepatocyte injury. On the opposite side, those who meet the NAFLD, but not the MAFLD definition, are normal-weight individuals with zero or just onecriterion for metabolic dysfunction, without other forms of liver disease and without significant alcohol consumption. Therefore, it is conceivable that these individuals may be characterized by a lower risk of both liver-related events and cardiovascular disease. Indeed, available studies found that patients with MAFLD are usually characterized by a higher prevalence of significant liver fibrosis and by a higher cardiovascular risk compared with patients with NAFLD[71]. On the other hand, the degree of concordance between the two definitions is related to the prevalence of other forms of liver disease (such as viral hepatitis) and significant alcohol consumption within the considered population[72]. For instance, in a study we performed based on data obtained in the general US population, where liver steatosis and fibrosis were evaluated through vibration-controlled transient elastography (VCTE), the degree of overlap was high (Cohen's κ 0.92)[73]. This was related to the low proportion of normal-weight individuals without metabolic alterations in people with steatosis (NAFLD-only), as well as to the low prevalence of viral hepatitis and (self-reported) significant alcohol consumption (MAFLD-only) in this setting. Moreover, we showed that none of the patients falling in the NAFLD-only group had evidence of advanced liver fibrosis either by VCTE or according to noninvasive serum biomarkers such as FIB-4 or NAFLD Fibrosis Score (NFS). Conversely, in a study performed in Japan, the degree of overlap between the two definitions was much lower. This was related to a much higher proportion of normal-weight individuals among patients with steatosis and a higher prevalence of significant alcohol consumption compared to the US[71]. Similar to our results, the Authors reported lower values of liver stiffness and noninvasive biomarkers of fibrosis in patients in the NAFLD-only group compared with the MAFLD-only group.

More recently, several studies compared NAFLD with MASLD. By definitions, in this case, the NAFLD-only group is characterized by normal-weight individuals without signs of metabolic dysfunction; on the other hand, few patients may be diagnosed with MASLD only if they have concomitant viral hepatitis (which is not considered as an exclusion criterion in the MASLD definition). Importantly, the degree of overlap between NAFLD and MASLD is even higher than between NAFLD and MAFLD, due to the exclusion of significant alcohol intake in both definitions. For instance, in a recent study from Sweden on a large cohort of patients diagnosed with NAFLD (most of whom have available data on liver histology), only 4 out of 1,333 (0.3%) did not meet the MASLD criteria[74]. The Authors, therefore, conclude that no further studies are necessary to evaluate the natural history of MASLD as it is superimposable to that of NAFLD; similarly, given the high degree of concordance of the two definitions, there is no need to re-evaluate the performance of noninvasive biomarkers of liver fibrosis compared with liver biopsy in patients with MASLD[75]. It should be noted, however, that these conclusions may not apply to different countries and regions, especially those with a high proportion of lean NAFLD patients.

In a recent study performed using data from the 2017-2020 NHANES database (representative of the overall US population), we showed that among participants with SLD, MASLD comprised the largest part (89.4%), followed by MetALD/ALD (7.7%), with a very low proportion of participants falling in the cryptogenic SLD category[76]. In a subsequent study performed in South Korea, MASLD accounted for approximately 75% of SLD cases, MetALD accounted for 20%, while 3.3% fell in the cryptogenic SLD category. Moreover, 95.80% of the NAFLD cases fulfilled the new criteria for MASLD[77,78]. In general, studies performed in Asian countries are more likely to identify participants with SLD that do not meet any metabolic dysfunction criteria and, therefore, fall in the cryptogenic SLD category (i.e., that can be diagnosed with NAFLD but not with MASLD). An interesting aspect of the new Delphi consensus is the introduction of a new disease entity called MetALD, which represents patients with coexisting metabolic dysfunction, steatosis, and significant alcohol intake. The introduction of this condition may represent a way to further study the impact of alcohol on different outcomes in the setting of SLD[79,80]. In our study, these patients were characterized by a higher FIB-4 score compared with patients with MASLD (as expected due to alcohol increasing the AST/ALT ratio), while no significant difference was present in the proportion of patients with elevated LSM[73]. More recently, a few cohort studies evaluated the association between MASLD, MetALD, and hard clinical outcomes such as all-cause mortality, cardiovascular events, and cancer-related mortality[81-84]. Most studies were performed in general population settings and used either imaging or noninvasive scores to identify steatosis. We summarized evidence from these studies in a systematic review and meta-analysis[85]. Briefly, compared with patients without SLD, both MASLD and MetALD were independently associated with a higher risk of cardiovascular disease and all-cause mortality. Importantly, MetALD was also associated with a higher risk of cancer-related mortality, while MASLD was not. Furthermore, Israelsen *et al.* showed that the risk of liver-related events increased progressively from MASLD to MetALD to ALD, stressing the importance of alcohol consumption on clinical outcomes throughout the spectrum of SLD[79].

Given that MASLD was recently introduced, studies comparing it to MAFLD are limited in number. There are two main differences between these definitions. First, while MAFLD includes patients with significant alcohol consumption, MASLD does not (as MetALD and ALD perform this task). Second, while both include patients with overweight/obesity or type 2 diabetes, the main difference applies to normal-weight individuals. While MASLD only needs one criterion for metabolic dysfunction, MAFLD needs two. Therefore, when comparing the features of patients in non-overlapping groups, those with MASLD-only are characterized by normal weight and a single metabolic abnormality[86]. It is conceivable that these patients (similarly to the NAFLD-only group) are at low risk for both liver-related events and cardiovascular mortality. As the two definitions differ mostly in the number of metabolic abnormalities that need to be

present in normal-weight individuals, a recent Indian study evaluated which definition performed better in this patient population[87]. The Authors included 170 patients with lean NAFLD. Among them, 142 (83.5%) fulfilled the MASLD definition, while only 84 (49.4%) patients satisfied the MAFLD criteria (even though data on HOMA-IR and hs-CRP were not available for most patients). According to the MAFLD definition, half of all lean NAFLD patients could not receive a specific diagnosis, while according to the recent Delphi consensus, 16.5% would be diagnosed with cryptogenic SLD. Unfortunately, genetic data were not available in this study. While the Authors carefully excluded patients with drug-induced liver injury, chronic viral hepatitis, malnutrition, celiac disease, and Wilson's disease, potential other etiologies were not evaluated. Nonetheless, it is unlikely that rare genetic metabolic disorders could account for all the remaining cases and the underlying pathophysiology of SLD in this small subgroup remains elusive.

On the opposite side, patients in the MAFLD-only group have a higher alcohol intake in the presence of metabolic dysfunction; this group should be characterized by a higher risk of liver-related events and probably cardiovascular outcomes, as suggested by a recent population-based study[88]. It should be noted, however, that by looking at the definitions, one can expect a high degree of overlap between this MAFLD-only group and patients with MetALD.

THE HURDLES OF DEFINING METABOLIC DYSFUNCTION

As recently reviewed[89], the history of the debate about metabolic health and metabolic dysfunction dates back at least to the 1988 Banting Lecture by Gerald Reaven, discussing the insulin resistance syndrome[90]. Several definitions of the metabolic syndrome have been proposed. While they all focus on the same cluster of variables (i.e., waist circumference, triglycerides, HDL-cholesterol, blood pressure and blood glucose levels), the number of alterations needed to make a diagnosis and the specific threshold to be applied for each component varied. The most frequently cited are the recommendations from the National Cholesterol Education Program (NCEP)-ATP III[91] published in 2001, later harmonized by Alberti *et al.*[92]. According to these definitions, metabolic syndrome can be diagnosed when the patient meets at least three of the five considered components. While the effort to achieve a global consensus on the definition of this prevalent condition is commended, relevant criticisms of the definition have been put forward by eminent Authors. First, this definition does not include any measure of insulin resistance, which is believed to be the pathophysiological defect underlying this cluster of manifestations[93]. Indeed, accurate measurement of insulin resistance would require performing the gold standard euglycemic, hyperinsulinemic clamp[94], which is time-consuming and elaborate and not well suited for large-scale application. Nonetheless, several easier-to-perform biomarkers based on fasting insulin and fasting glucose levels, such as HOMA-IR, QUICKI, and their variations, have been proposed[95-98]. They exhibit moderate performance compared to the glucose clamp technique[99], but still need measurement of insulin levels, which are somewhat assay-dependent[100]; consequently, measurement of insulin resistance is not recommended by most international guidelines in any specific condition. Second, while metabolic syndrome needs three metabolic alterations to be present and define a yes/no condition, evidence shows that the risk for cardiovascular disease and mortality increases progressively with the increasing number of metabolic alterations present, without a specific cut-off[101]. Another interesting aspect is related to the impact of different metabolic risk factors on liver-related outcomes. In a recent large cohort study conducted in patients with T2D, the comorbidity with the largest association with incident major adverse liver outcomes (MALOs) was hypertension (aHR 2.06, 95%CI: 1.57–2.71), while dyslipidemia, obesity, and albuminuria contributed to a lesser extent[102]. The study confirmed that the higher the number of traits of metabolic syndrome present, the higher the risk of MALOs.

Finally, some perceive metabolic syndrome as a way to medicalize people who do not fit the criteria for well-defined conditions such as hypertension or diabetes mellitus.

Given these premises, it does not come as a surprise that the definition of metabolic dysfunction differs between MASLD and MAFLD. The MAFLD criteria were clearly based on the metabolic syndrome criteria, but they introduced insulin resistance (HOMA-IR) and low-grade inflammation (hs-CRP) as novel contributors[103]. Indeed, these two aspects play pivotal roles in the development and progression of chronic metabolic conditions including liver steatosis and their inclusion aims at reminding clinicians of this aspect. Nonetheless, the main criticism of this approach is related to the fact that these biomarkers are seldom (if not never) measured in routine clinical practice.

The other aspect that has been subject to debate is whether BMI-based definitions of overweight and obesity (which are considered by both MAFLD and MASLD) are enough to define disease. Indeed, a recent report from Korea using magnetic resonance showed that a quarter of patients with MAFLD were "metabolically healthy" (≤ 1 risk factor and no diabetes), and more than half did not have metabolic syndrome[104]. The concept of metabolically healthy obesity was fueled by several studies showing similar mortality rates in patients with overweight/obesity without metabolic syndrome, compared to normal-weight individuals[105-107]. Moreover, a frequently cited meta-analysis published in 2013 did not show any increased risk of all-cause mortality in patients with grade I obesity (0.95, 95%CI: 0.88-1.01) and even a reduced risk of death in people with overweight (HR 0.94, 95%CI: 0.91-0.96)[108]. These results provided evidence for the so-called "obesity paradox", i.e., the observation that among patients with a specific health condition, those with higher BMIs might have a prognostic benefit[109,110]. Nonetheless, these results have been questioned more recently. For instance, a subsequent large meta-analysis including more than 10 million individuals from > 200 studies performed across the globe showed that all-cause mortality was minimal in the 20-25 kg/m^2 group, while both people in the overweight (1.07, 1.07–1.08 for BMI 25.0-27.5 kg/m^2; 1.20, 1.18–1.22 for BMI 27.5–30.0 kg/m^2) and those in the class I obesity (1.45, 95%CI: 1.41–1.48) groups had higher mortality rates[111]. Subsequent studies showed that, while the prognosis of metabolically healthy obese (MHO) individuals might be better compared with metabolically unhealthy (MUO) patients, their overall risk of dying is higher than that of metabolically healthy normal-weight individuals[112]. Furthermore, it is highly likely that the MHO phenotype, although not rare in the general population (especially among young women), is a transient state, with many patients (especially if they do not lose significant amounts of weight) switching to a MUO phenotype with increasing age[113]. For this reason, even recognizing the limitations associated with BMI as a measure of overall adiposity, we agree with the inclusion of overweight/obesity as a diagnostic criterion.

CONCLUSION

In conclusion, we believe that the recent debate on the best terminology and diagnostic criteria in the field of liver steatosis fueled an interesting debate and led to increased awareness of this condition among clinicians[114]. The major advantage of the new definitions is their acknowledgment of the strict association between liver steatosis and metabolic factors, leading some Authors in the past to consider SLD as the hepatic manifestation of the metabolic syndrome[115]. While clinicians might be confused by subtle changes in the acronyms and related disease definitions, evidence shows that several aspects should be kept in mind, regardless of terminology. First, the higher the number of concomitant metabolic abnormalities, the higher the risk of both liver-related and cardiovascular-related mortality. Second, whether or not it interferes with diagnostic criteria, careful evaluation for potential coexisting chronic liver conditions is of great prognostic importance. Third, notwithstanding the limitations related to its estimation, evaluation of alcohol intake should be performed in all patients with SLD and alcohol intake should be limited to a minimum (if not

completely eliminated) in this patient population. On this point, future studies evaluating the natural history of MetALD compared with MASLD might shed more light on whether thresholds for alcohol consumption have a strong evidence base.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study and performed data analysis and interpretation: Ciardullo S, Perseghin G

Performed data acquisition and provided administrative, technical, and material support: Ciardullo S, Perseghin G

Availability of data and materials

Not applicable.

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Conflicts of interest

Stefano Ciardullo is a Junior Editorial Board member of the journal *Metabolism and Target Organ Damage*. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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