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A new definition for metabolic dysfunction-associated fatty liver disease

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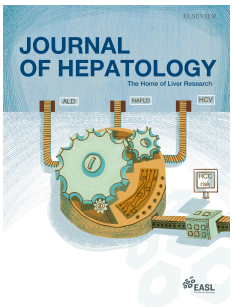

A new definition for metabolic associated fatty liver disease: an international expert consensus statement

Mohammed Eslam, Philip N. Newsome, Quentin M. Anstee, Giovanni Targher, Manuel Romero Gomez, Shira Zelber-Sagi, Vincent Wai-Sun Wong, Jean-François Dufour, Jörn Schattenberg, Marco Arrese, Luca Valenti, Gamal Shiha, Claudio Tiribelli, Hannele Yki-Järvinen, Jian-Gao Fan, Henning Gronbaek, Yusuf Yilmaz, Helena Cortez-Pinto, Claudia P. Oliveira, Pierre Bedossa, Leon A. Adams, Ming-Hua Zheng, Yasser Fouad, Wah-Kheong Chan, Nahum Mendez-Sanchez, Sang Hoon Ahn, Laurent Castera, Elisabetta Bugianesi, Vlad Ratziu, Jacob George

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A new definition for metabolic associated fatty liver disease: an international expert consensus statement

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Brief summary

The exclusion of other chronic liver diseases including “excess” alcohol intake has till now been necessary to establish a diagnosis of metabolic-dysfunction-associated fatty liver disease (MAFLD). However, given our current understanding of the pathogenesis of MAFLD and its rising prevalence, “positive criteria” to diagnose the disease are required. In this work, a panel of international experts from 22 countries propose a new definition that is both comprehensive yet simple for the diagnosis of MAFLD and is independent of other liver diseases. The criteria are based on evidence of hepatic steatosis, in addition to one of the following three criteria, namely overweight/obesity, presence of type 2 diabetes mellitus, or evidence of metabolic dysregulation. We propose that disease assessment and stratification of severity should extend beyond a simple dichotomous classification to steatohepatitis versus non-steatohepatitis. The group also suggests a set of criteria to define MAFLD associated cirrhosis and proposes a conceptual framework to consider other causes of fatty liver disease. Finally, we bring clarity to the distinction between diagnostic criteria and inclusion criteria for research studies and clinical trials. Reaching consensus on the criteria for MAFLD will help unify the terminology (e.g. for ICD-coding), enhance the legitimacy of clinical practice and clinical trials, improve clinical care and move the clinical and scientific field of liver research forward.

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Introduction

Metabolic-dysfunction-associated fatty liver disease (MAFLD), formerly named non-alcoholic fatty liver disease (NAFLD), affects about a quarter of the world's adult population, poses a major health and economic burden to all societies [1-3] and yet has no approved pharmacotherapy. The high prevalence of this disease has been fuelled by the rapid rise in levels of sedentary behaviour, low levels of physical activity, excess high calorie energy intake relative to expenditure in nutritionally imbalanced and unhealthy diets [4]. In parallel, the prevalence of poor metabolic health in adults of affluent countries is high, even in normal weight individuals [5, 6]. In this context of high risk and prevalence, the lack of a clear nomenclature for liver disease not due to alcohol use disorder alongside the absence of defined clinical criteria for a "positive" diagnosis of this disease constitute urgent unmet needs in the field.

To tackle this challenge, an international panel of experts have detailed the rationale for an update of the nomenclature and metabolic associated fatty liver disease, MAFLD, has been proposed as a more appropriate term to describe the liver disease associated with the known metabolic dysfunction [1, 7]. MAFLD, as with the previous term NAFLD, represents the hepatic manifestation of a multisystem disorder, which is heterogeneous in its underlying causes, presentation, course and outcomes [8]. However, given its complex pathophysiology, it is unlikely that a single diagnostic test will become available and new diagnostic criteria will need to be developed to define MAFLD, as was the case for the metabolic syndrome, which notably has multiple definitions [5, 9-14]. Until now the exclusion of other chronic liver diseases, including "excess" alcohol intake, was necessary for the diagnosis of MAFLD. As the pathogenic process leading to MAFLD is now better understood and is seen to

originate from an underlying state of systemic metabolic dysfunction, MAFLD is perceived as a standalone disease which warrants a positive diagnosis, rather than a "none"-disease rubric. Moreover, the rising prevalence of MAFLD makes its coexistence with other chronic liver diseases quite possible, further negating a diagnosis based on exclusion of concomitant diseases. It is therefore our belief that this disease needs to be defined by its own set of positive criteria, rather than by exclusion criteria.

Hence, in this work we propose a comprehensive, yet simple, set of criteria for the diagnosis of MAFLD that are independent of the amount of alcohol consumed and can be applied to patients in any clinical setting. We also bring clarity to the diagnostic criteria, which are distinct from inclusion criteria for research studies and clinical trials. The long-term impact will be to promote wider discussion, help clinicians in routine clinical care, allow comparison of different studies, assist regulatory agencies and other stakeholders in case definition for clinical trials, and facilitate documentation in the International Classification of Diseases (ICD) systems and Disease-Related Groups (DRG). The inclusion and endpoints of clinical trials that have been the focus of multiple other initiatives will likely evolve as acceptance of the new nomenclature and definition progresses [15].

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Criteria for a diagnosis of MAFLD

Presently the definition of NAFLD as reported in most guidelines and recent publications is based on the presence of steatosis in >5% of hepatocytes in the absence of significant ongoing or recent alcohol consumption and other known causes of liver disease [15-18]. Herein we propose a set of new "positive" criteria for the diagnosis of MAFLD regardless of alcohol consumption or other concomitant liver diseases.

Suggestion:

The proposed criteria for a positive diagnosis of MAFLD are based on histological (biopsy), imaging or blood biomarker evidence of fat accumulation in the liver (hepatic steatosis) in addition to one of the following three criteria, namely overweight/obesity, presence of type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation. The latter is defined by the presence of at least two metabolic risk abnormalities, listed in **Table 1**. A flowchart for the proposed diagnostic criteria is depicted in **Figure 1**.

For detection of steatosis, ultrasound is the most widely used first-line diagnostic modality and is recommended. It should be noted that ultrasound has limited sensitivity, it does not reliably detect steatosis when <20%, and its performance is sub-optimal in subjects with body mass index (BMI) >40 kg/m^2. FibroScan vibration-controlled transient elastography controlled attenuation parameter (CAP) (or similar) which is increasingly undertaken in routine clinical practice has a reported area under the area under the receiver-operating-characteristic curve (AUROCs) of 0.70 for steatosis, using biopsy analysis as the reference standard [19]. Computed tomography (CT) or magnetic resonance imaging (MRI) if available can be used to diagnose moderate and severe steatosis. Magnetic resonance spectroscopy (MRS) provides a quantitative estimation of liver fat, but it is expensive, has limited availability, and requires special software. Therefore, magnetic resonance imaging–derived proton density fat fraction (MRI-PDFF) which is in close agreement with MRS but is more practical is generally preferred in clinical trials [20]. Pending appropriate validation from future research, serum biomarkers of steatosis could replace imaging methods. However, currently, this would only be appropriate for large epidemiological studies with markers such

as fatty liver index (FLI), given data available so far for the diagnostic and prognostic performance of FLI [15-18].

Rationale:

Although there is no general consensus on the criteria to define ‘‘metabolic health” that indicates a high or low health risk of cardiometabolic disease, a number of guidelines have evidence-based recommendations for risk assessment. The criteria for defining “metabolic health” status are commonly based on the metabolic syndrome definition proposed by the Adult Treatment Panel III [5, 9-14].

The rationale for excess body weight as one of the three criteria for defining MAFLD (**Figure 1**) stems from the fact that it has strong pathological link to MAFLD and it is a critical determinant of adverse clinical outcomes. A recent meta-analysis of 239 prospective studies that controlled for multiple confounding factors demonstrated that both overweight and obesity are associated with higher all-cause mortality compared to a normal body weight (defined as a body mass index [BMI] of 18.5–<25.0 kg/m^2 in Caucasian individuals) [21]. Although obesity can be classified as metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUHO) [22, 23] with purported differential impacts on risk of cardiovascular outcomes, large-scale cohort studies do not support the notion that individuals with MHO, at least as currently defined, are protected from the development of cardiometabolic complications [24-26]. Similarly, a recent report demonstrated that MHO subjects with MAFLD remain at high risk for the development of significant hepatic fibrosis [27]. Thus, the presence of both excess weight and metabolic dysfunction have independent effects on risk of MAFLD and cardiometabolic outcomes. As MAFLD is commonly seen in clinical practice in association with overweight/obesity, this criterion would identify most patients in routine care (as opposed to those in clinical research and cohort studies).

Similarly, an intimate association between MAFLD and type 2 diabetes mellitus (T2DM) has been demonstrated; >70% of patients with T2DM have MAFLD [28, 29]. This criterion can also be applied in clinical practice (**Figure 1**).

In addition, the presence of steatosis with at least two metabolic risk abnormalities mentioned in **Table 1/ Figure 1** should be a criterion to diagnose MAFLD in non-overweight/obese subjects. Lean individuals likewise are not protected from the development of MAFLD [2, 4, 30] and it is recognised that 6-20% of patients with MAFLD are neither overweight nor obese [30, 31]. Indeed, in a recent study of 1000 liver biopsies in MAFLD subjects, the histological severity of disease in patients with BMI < 23 kg/m^2 was no different to that in than those with BMI >25 kg/m^2 [32]. There is also growing evidence for the importance of metabolic health extending beyond what is reflected by definitions of obesity. It has for instance been demonstrated that regardless of BMI, metabolically unhealthy individuals have higher cardiovascular disease risk than their metabolically healthy counterparts [26]. It should be noted that metabolically unhealthy lean patients may have greater ectopic fat accumulation, predominately in a visceral distribution [5]. Consistently, metabolically unhealthy non-obese patients with MAFLD are at greater risk of liver damage and cardiovascular risk compared to metabolically healthy individuals [27]. To complicate matters further, metabolic health is a dynamic state across the life span and determinants for the conversion from metabolically healthy to unhealthy phenotypes needs to be considered [33]. Some studies suggest that liver fat accumulation is a very sensitive and early indicator of metabolic dysfunction [34, 35]. Thus the proposed criteria would be able to capture the whole phenotypical spectrum from metabolically unhealthy normal weight to metabolically unhealthy obesity.

MAFLD: a single overarching term

Suggestion:

MAFLD should be the single overarching term to describe the disease. Disease severity should be best described by the grade of activity and the stage of fibrosis. This is similar to what is accepted for other chronic liver diseases and recognises that MAFLD activity grade is a continuum [36]. This should replace the current dichotomous stratification into steatohepatitis and non-steatohepatitis which has limitations that are discussed below.

Rationale:

There is no doubt that the transition from steatosis to steatohepatitis is a cardinal feature for the progressive liver disease that leads to cirrhosis and cancer. For instance, progression from steatosis alone or steatosis with mild inflammation to bridging fibrosis has been shown to occur concurrently with the transition through steatohepatitis [37]. Beyond this qualitative association, several longitudinal studies, both natural history-based and interventional, have demonstrated a semiquantitative relationship between disease activity (grade of steatohepatitis) and changes in fibrosis. Increases in activity grade, as measured by the commonly used histological NAFLD Activity Score (NAS), which grades steatosis in addition to inflammation and liver cell injury, were shown to be associated with fibrosis progression while reduction of activity grade was associated with fibrosis regression despite steatohepatitis persistence [38-41]. Pharmacological interventions and long-term observational natural history studies have shown the same directionality between activity grade, hepatic inflammatory changes and fibrosis progression/regression [40, 42].

The aforementioned findings suggest that a dichotomous classification to NASH or not-NASH may not capture the full spectrum of the disease course in response to changes in the underlying metabolic dysfunction or to pharmacological interventions. Therefore we propose

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that rather than a dichotomous classification (steatosis vs steatohepatitis) the disease process in MAFLD is best described by the grade of activity and the stage of fibrosis [43].

From a clinical and pathological concept, this suggestion should result in improved case identification, while sub-classification may capture histological changes in disease status with relevant impacts on the disease course. Ultimately, future non-invasive tests capturing both disease activity and fibrosis stage should aim at making disease categorization possible and reserve the use of liver biopsy for complicated cases such as ruling out other forms of liver disease, or further characterization of the disease process, particularly that the pathology score represents not only "amount" but also location and parenchymal alteration, e.g. vascular alterations.

MAFLD cirrhosis – no longer a cryptogenic cirrhosis

Suggestion:

We propose that patients with cirrhosis with low or undetectable levels of steatosis and who meet the proposed diagnostic criteria for MAFLD should be considered under the umbrella of MAFLD, as MAFLD related cirrhosis. The term “cryptogenic cirrhosis” in this group should be avoided.

The proposed diagnostic criteria for MAFLD-related cirrhosis are patients with cirrhosis in the absence of typical histological signs suggestive of steatohepatitis who meet at least one of the following criteria: past or present evidence of metabolic risk factors that meet the criteria to diagnose MAFLD, as described above (**Table 1**) with at least one of the following 2) documentation of MAFLD on a previous liver biopsy, 2) historical documentation of steatosis by hepatic imaging (**Table 2**). Notably, a history of past alcohol intake should be considered as patients may have a dual disease aetiology with alcohol use disorder, as detailed below.

Rationale:

Growing evidences suggests that “cryptogenic cirrhosis” and “MAFLD cirrhosis” are two distinct entities that have different liver-related outcomes and should not be lumped together [44-46]. In some patients with cirrhosis from fatty liver disease, steatosis may be absent. However, these patients should be considered as part of the spectrum of MAFLD as they have the same risk factors for liver disease as patients with typical MAFLD related cirrhosis and therefore likely the same pathogenic drivers of metabolic dysfunction. Most likely, these patients are simply diagnosed at a later stage when typical histological signs of steatosis, inflammation and hepatocyte injury have vanished.

Dual aetiology: concomitant MAFLD with other liver diseases

Suggestion:

Exclusion of alcohol-associated fatty liver disease (ALD) based on current criteria for alcohol use disorder [47], viral infections (human immunodeficiency virus (HIV), hepatitis B virus, hepatitis C virus), drug-induced liver injury (DILI), autoimmune hepatitis either at baseline or at follow-up is not a prerequisite criterion for diagnosis. Patients who meet the criteria to diagnose MAFLD as described above and who also have one of these concomitant conditions should be defined as having dual (or more) aetiology fatty liver disease [48] (**Table 3**).

Rationale:

With the dramatic rise in the global prevalence of MAFLD, it can and frequently does coexist with other conditions such as viral hepatitis and ALD [49-51]. These individuals likely have a different natural history and response to therapy [52-54] than those with liver disease of a

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single aetiology. Moreover, the current recommended cut-offs to define significant alcohol consumption as well as the duration of alcohol withdrawal in those with suspected MAFLD are arbitrary [55]. Adding to the complexity, the low reliability of the current diagnostic methods, such as patient interviews and serum biomarkers, the fact that patients usually underestimate their alcohol consumption, and the lack of standardisation of terminology such as “social” and “binge” drinking [56] renders it hard to ascertain true alcohol consumption and its long-term impact on liver disease. We believe that the greatest benefit of a dual aetiology criterion compared with previous guidelines is that MAFLD will no longer be a diagnosis of exclusion. Instead, exclusion of significant alcohol intake through patient interview aids in diagnosis but is not required because dual aetiology is possible and even frequent[48].

Disease sub-phenotyping

MAFLD may, in the future, be sub-classified based on new knowledge that might indicate the predominant pathophysiological pathway that drives the development of a morphologically limited set of histological features (steatosis, ballooning, inflammation and fibrosis) but which leads to different clinical outcomes. Such sub-classification will be particularly valuable for MAFLD given its substantial heterogeneity [57-59]. Thus, while we suggest the umbrella term MAFLD, it is in the knowledge that further sub-classification will likely ensue. Sub classification for example may encompass the role of genetic variants such as *Patatin-like phospholipase domain-containing protein 3 (PNPLA3), Transmembrane 6 superfamily 2 (TM6SF2), membrane bound O-acyltransferase domain containing 7 (MBOA7) and hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13),* and epigenetic or other modifiers of disease. This recognises the fact that MAFLD represents a complex disease trait that may be

influenced by a range of independent modifiers that individually may be insufficient to cause disease, as recently reviewed [1, 58].

A likely consequence of implementation of the proposed for diagnosing MAFLD will also highlight a new category of fatty liver disease, including a relative minority of patients previously deemed as affected by NAFLD, that is not MAFLD, neither apparently alcohol associated, nor to known uncommon causes [30, 60]. This may foster new discoveries into the causes, mechanisms, classification and treatment of fatty liver disease.

Alternative causes of fatty liver disease

Suggestion:

We suggest that the terms “primary” and secondary” hepatic steatosis are avoided because all pathological processes are secondary. Instead, we propose use of “alternate causes” of fatty liver disease to describe the latter that includes conditions such as: medications (corticosteroids, valproic acid, tamoxifen, methotrexate, and amiodarone), coeliac disease, starvation, total parenteral nutrition, severe surgical weight loss or disorders of lipid metabolism (abetalipoproteinemia, hypobetalipoproteinemia, lysosomal acid lipase deficiency(LAL), familial combined hyperlipidaemia, lipodystrophy, Weber–Christian syndrome, glycogen storage disease, Wilson disease). These may be associated with metabolic dysfunction (MAFLD) or be present with other triggers of less frequent forms of fatty liver disease.

Rationale:

The classification of steatosis into primary and secondary is misleading, anachronistic, and indeed does not consider that hepatic steatosis >5% is not physiological and must be secondary to dysfunction of multiple pathways regulating lipid entry, synthesis and oxidation, and excretion. Alternative causes of hepatic steatosis recognises the existence of these less frequent causes of steatosis while acknowledging that MAFLD represents the overwhelming majority of cases of hepatic steatosis seen in clinical practice.

The distinction between diagnostic criteria and inclusion criteria for clinical trials

Diagnostic criteria for clinical purposes in any disease or syndrome are distinct from inclusion criteria for clinical studies or trials, at least with regard to their intended purpose (**Supplementary Table 1**). Diagnostic criteria generally are a set of symptoms, signs and tests used in routine clinical care to broadly reflect the features of a disease. The aim is to identify individuals with the condition, as accurately as possible in order to guide their management. Inclusion criteria for trials or studies by contrast are the main attributes of a study target population that the investigators will utilise to address their research question [61]. The differences between diagnostic and inclusion criteria will depend on a variety of factors, including the study or trial design. The "distance" between diagnostic and inclusion criteria depends on a variety of factors including the study or trial design or specifics of drug mechanism of action but not necessarily on clinical features of common patients presenting to the clinics. Thus, setting definitions for MAFLD based on "positive" criteria and the exclusion of patients with fatty liver unrelated to metabolic dysfunction (with fatty liver but not MAFLD) will render study cohorts more homogeneous thereby increasing the likelihood of detecting a significant impact of clinical approaches targeting MAFLD.

Every clinical trial poses a unique set of requirements/criteria (inclusions/exclusions) for participating individuals. In this context, the decision to include patients with dual aetiology (e.g., those with MAFLD and alcohol intake, irrespective of the amount of alcohol that is allowed, current or past alcohol consumption etc.,) is dependent entirely on the clinical trial designer. In trials seeking to test the mechanism of action of a drug for example, more stringent inclusion criteria might be necessary. These considerations in no way detract from the conduct of the trial, nor does it affect the diagnostic criteria proposed for MAFLD. The analogous situation is evident in viral hepatitis in which patient recruitment for treatment trials required the presence of viraemia but included also patients with various limits of alcohol intake or undertook analyses based on insulin resistance criteria.

Multiple recent reports suggest that enrolling patients for MAFLD clinical trials is particularly challenging, with various pharmaceutical companies having to delay or scale back ongoing trials due to recruitment difficulties. However, rather than simply adding more sites, innovative strategies could help to expedite recruitment. Based on the conceptualised diagnostic criteria above and the reality of the real-world patient landscape, we need to consider a more pragmatic approach to target patients with MAFLD with potentially a higher threshold of alcohol intake than currently used. Furthermore, with the very high prevalence of MAFLD and alcohol intake worldwide, the relatedness between any current study population and real-world populations is of concern. Indeed, although very desirable, hepatology faces unique challenges in discriminating between pure alcohol associated and pure metabolic dysfunction disorders with similar manifestations and overlapping features. Lessons can be learned from the viral hepatitis field with revolutionary changes being brought about by the impact of direct-acting antiviral agents such that clinical trials moved to explore the benefit of therapy in HIV-HCV co-infected patients and in subgroups with mixed cryoglobulinemia.

Conclusion

In this consensus, an international panel of experts propose clear and simple criteria for a diagnosis of MAFLD that shifts it from a disease of exclusion to one of inclusion. The diagnosis is based on recognition of underlying abnormalities in metabolic health with acceptance that MAFLD may commonly co-exist with other conditions (**Figure 1**). We believe that the proposed diagnostic criteria are novel and practical. Future research will involve an iterative process of clinical validation of the criteria in prospective studies, confirming the feasibility of the criteria to level the clinical trial recruitment field and most importantly, utility in routine clinical practice. We acknowledge that other initiatives are required to sub-phenotype patients with MAFLD, and fatty liver disease in general, in order to drive precision patient management and create effective pathways between primary care and liver clinics. Finally, reaching consensus on the criteria for MAFLD will also help unify the terminology (e.g. for ICD-coding), to enhance the legitimacy of clinical practice and clinical trials, to improve clinical care and to move the clinical and scientific field of Hepatology forward.

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Figure 1: Flowchart for the proposed "positive" diagnostic criteria for MAFLD.

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Table 1: Criteria defining metabolic risk factors

Increased cardiometabolic and MAFLD risk defined presence of at least two of the following metabolic at-risk criteria:

- Waist circumference ≥102/88 cm in Caucasian men and women or ≥90/80 cm in Asian men and women)*.
- Blood pressure ≥130/85 mmHg or specific drug treatment.
- Plasma triglycerides ≥150 mg/dL (≥1.70 mmol/l) or specific drug treatment.
- Plasma HDL-cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment.
- Prediabetes (i.e., fasting glucose levels 100 to 125 mg/dL (5.6 to 6.9 mmol/L), or 2-hour post-load glucose levels 140 to 199 mg/dL (7.8 to 11.0 mmol) or HbA1c 5.7% to 6.4% (39–47 mmol/mol)).
- Homeostasis model assessment (HOMA)-insulin resistance score ≥2.5.
- Plasma high-sensitivity C-reactive protein (hs-CRP) level >2 mg/L.

* The AHA/NHLBI guidelines for metabolic syndrome recognize an increased risk for cardiovascular disease and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 cm in women and identify these as optional cut points for Caucasian individuals or populations with increased insulin resistance (13).

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Table 2: Criteria for a diagnosis of MAFLD related cirrhosis

Patients with cirrhosis in the absence of typical histology who meet at least one of the following criteria:

Past or present evidence of metabolic risk factors that meet the criteria to diagnose MAFLD, as described in Table 1, with at least one of the following:
1) Documentation of MAFLD on a previous liver biopsy*.
2) Historical documentation of steatosis by hepatic imaging*.

**History of past alcohol intake should be considered as patients may have a dual disease aetiology with alcohol use disorder*

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Table 3: Dual aetiology fatty liver disease (concomitant MAFLD and other liver disease)

Meeting the criteria for a diagnosis of MAFLD **Plus** Any other cause for liver disease e.g., alcohol-use disorder defined as consumption of >3 drinks per day in men and >2 drinks per day in women, or binge drinking (defined as >5 drinks in males and >4 drinks in females, consumed over a 2- hour period)*, as defined by the National Institute of Alcoholism and Alcohol Abuse [47, 62], viral infection (HIV, HBV and HCV), autoimmune hepatitis, inherited liver disorders, DILI or other known liver disease. * *These thresholds are derived from quantities beyond which a person is at more risk for alcohol related liver disease and may be in excess of the quantity needed to modify disease progression in MAFLD. This requires further study.*

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References

[1] Eslam M, Sanyal AJ, George J. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020.

[2] Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastro Hepat 2018;15:11-20.

[3] Sarin SK, Kumar M, Eslam M, George J, Al Mahtab M, Akbar SMF, et al. Liver diseases in the Asia-Pacific region: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol 2019.

[4] Inoue Y, Qin B, Poti J, Sokol R, Gordon-Larsen P. Epidemiology of Obesity in Adults: Latest Trends. Curr Obes Rep 2018;7:276-288.

[5] Stefan N, Schick F, Haring HU. Causes, Characteristics, and Consequences of Metabolically Unhealthy Normal Weight in Humans. Cell Metab 2017;26:292-300.

[6] Araujo J, Cai J, Stevens J. Prevalence of Optimal Metabolic Health in American Adults: National Health and Nutrition Examination Survey 2009-2016. Metab Syndr Relat Disord 2019;17:46-52.

[7] Eslam M, Sanyal AJ, George J. Toward More Accurate Nomenclature for Fatty Liver Diseases. Gastroenterology 2019;157:590-593.

[8] Byrne CD, Targher G. NAFLD: A multisystem disease. Journal of Hepatology 2015;62:S47-S64.

[9] Cleeman JI, Grundy SM, Becker D, Clark LT, Cooper RS, Denke MA, et al. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Jama-J Am Med Assoc 2001;285:2486-2497.

[10] Black H, Cushman W, Green L, Izzo Jr J, Jones D, Materson B, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-2572.

[11] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 2005;112:2735-2752.

[12] Alberti K, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation 2009;120:1640-1645.

[13] Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127-e248.

[14] Association AD. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. Diabetes Care 2018;41:S13-S27.

[15] Siddiqui MS, Harrison SA, Abdelmalek MF, Anstee QM, Bedossa P, Castera L, et al. Case definitions for inclusion and analysis of endpoints in clinical trials for nonalcoholic steatohepatitis through the lens of regulatory science. Hepatology 2018;67:2001-2012.

[16] European Association for the Study of the L, European Association for the Study of D, European Association for the Study of O. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-1402.

[17] Wong VW, Chan WK, Chitturi S, Chawla Y, Dan YY, Duseja A, et al. Asia-Pacific Working Party on Non-alcoholic Fatty Liver Disease guidelines 2017-Part 1: Definition, risk factors and assessment. J Gastroenterol Hepatol 2018;33:70-85.
[18] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-357.
[19] Eddowes PJ, Sasso M, Allison M, Tsochatzis E, Anstee QM, Sheridan D, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology 2019;156:1717-1730.
[20] Caussy C, Reeder SB, Sirlin CB, Loomba R. Noninvasive, Quantitative Assessment of Liver Fat by MRI-PDFF as an Endpoint in NASH Trials. Hepatology 2018;68:763-772.
[21] Di Angelantonio E, Bhupathiraju SN, Wormser D, Gao P, Kaptoge S, de Gonzalez AB, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet 2016;388:776-786.
[22] Shea JL, Randell EW, Sun GA. The Prevalence of Metabolically Healthy Obese Subjects Defined by BMI and Dual-Energy X-Ray Absorptiometry. Obesity 2011;19:624-630.
[23] Munoz-Garach A, Cornejo-Pareja I, Tinahones FJ. Does Metabolically Healthy Obesity Exist? Nutrients 2016;8.
[24] Eckel N, Li Y, Kuxhaus O, Stefan N, Hu FB, Schulze MB. Transition from metabolic healthy to unhealthy phenotypes and association with cardiovascular disease risk across BMI categories in 90 257 women (the Nurses' Health Study): 30 year follow-up from a prospective cohort study. Lancet Diabetes Endocrinol 2018;6:714-724.
[25] Caleyachetty R, Thomas GN, Toulis KA, Mohammed N, Gokhale KM, Balachandran K, et al. Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women. J Am Coll Cardiol 2017;70:1429-1437.
[26] Lassale C, Tzoulaki I, Moons KGM, Sweeting M, Boer J, Johnson L, et al. Separate and combined associations of obesity and metabolic health with coronary heart disease: a pan-European case-cohort analysis. Eur Heart J 2018;39:397-406.
[27] Ampuero J, Aller R, Gallego-Duran R, Banales JM, Crespo J, Garcia-Monzon C, et al. The effects of metabolic status on non-alcoholic fatty liver disease-related outcomes, beyond the presence of obesity. Aliment Pharm Ther 2018;48:1260-1270.
[28] Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among a Largely Middle-Aged Population Utilizing Ultrasound and Liver Biopsy: A Prospective Study. Gastroenterology 2011;140:124-131.
[29] Arrese M, Barrera F, Triantafilo N, Arab JP. Concurrent nonalcoholic fatty liver disease and type 2 diabetes: diagnostic and therapeutic considerations. Expert Rev Gastroenterol Hepatol 2019;13:849-866.
[30] Chen F, Esmaili S, Rogers G, Bugianesi E, Petta S, Marchesini G, et al. Lean NAFLD: A Distinct Entity Shaped by Differential Metabolic Adaptation. Hepatology 2019.
[31] Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2017.
[32] Rastogi A, Shasthry SM, Agarwal A, Bihari C, Jain P, Jindal A, et al. Non-alcoholic fatty liver disease - histological scoring systems: a large cohort single-center, evaluation study. APMIS 2017;125:962-973.
[33] Cho YK, Kang YM, Yoo JH, Lee J, Park JY, Lee WJ, et al. Implications of the dynamic nature of metabolic health status and obesity on risk of incident cardiovascular events and mortality: a nationwide population-based cohort study. Metabolism 2019;97:50-56.

[34] Bril F, Barb D, Portillo-Sanchez P, Biernacki D, Lomonaco R, Suman A, et al. Metabolic and Histological Implications of Intrahepatic Triglyceride Content in Nonalcoholic Fatty Liver Disease. Hepatology 2017;65:1132-1144.
[35] Rotman Y, Neuschwander-Tetri BA. Liver Fat Accumulation as a Barometer of Insulin Responsiveness Again Points to Adipose Tissue as the Culprit. Hepatology 2017;65:1088-1090.
[36] McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: Implications for prognosis and clinical management. Journal of Hepatology 2015;62:1148-1155.
[37] Pais R, Charlotte F, Fedchuk L, Bedossa P, Lebray P, Poynard T, et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatol 2013;59:550-556.
[38] Vilar-Gomez E, Calzadilla-Bertot L, Wong VWS, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology 2018;155:443-+.
[39] Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, et al. The natural history of nonalcoholic fatty liver disease: A population-based cohort study. Gastroenterology 2005;129:113-121.
[40] Kleiner DE, Brunt EM, Wilson LA, Behling C, Guy C, Contos M, et al. Association of Histologic Disease Activity With Progression of Nonalcoholic Fatty Liver Disease. Jama Netw Open 2019;2.
[41] Brunt EM, Kleiner DE, Wilson LA, Sanyal AJ, Neuschwander-Tetri BA, Steatohepatitis N. Improvements in Histologic Features and Diagnosis Associated With Improvement in Fibrosis in Nonalcoholic Steatohepatitis: Results From the Nonalcoholic Steatohepatitis Clinical Research Network Treatment Trials. Hepatology 2019;70:522-531.
[42] Ratziu V, Harrison SA, Francque S, Bedossa P, Anstee QM, Ben S, et al. ALT as a non-invasive biomarker of histological response to pharmacotherapy in NASH patients: insights from the elafibranor GOLDEN505 trial. 67th Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2016; 2016: Newcastle University; 2016.
[43] Dufour JF. Time to Abandon NASH? Hepatology 2016;63:9-10.
[44] Thuluvath PJ, Kantsevoy S, Thuluvath AJ, Savva Y. Is cryptogenic cirrhosis different from NASH cirrhosis? Journal of Hepatology 2018;68:519-525.
[45] Caldwell S, Marchesini G. Cryptogenic vs. NASH-cirrhosis: The rose exists well before its name.... Journal of Hepatology 2018;68:391-392.
[46] Younossi Z, Stepanova M, Sanyal AJ, Harrison SA, Ratziu V, Abdelmalek MF, et al. The conundrum of cryptogenic cirrhosis: Adverse outcomes without treatment options. Journal of Hepatology 2018;69:1365-1370.
[47] Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG Clinical Guideline: Alcoholic Liver Disease. Am J Gastroenterol 2018;113:175-194.
[48] Boyle M, Masson S, Anstee QM. The bidirectional impacts of alcohol consumption and the metabolic syndrome: Cofactors for progressive fatty liver disease. J Hepatol 2018;68:251-267.
[49] Brunt EM, Ramrakhiani S, Cordes BG, Neuschwander-Tetri BA, Janney CG, Bacon BR, et al. Concurrence of histologic features of steatohepatitis with other forms of chronic liver disease. Modern Pathol 2003;16:49-56.
[50] Sanchez-Munoz D, Castellano-Megias VM, Romero-Gomez M. Histologic features of steatohepatitis in patients with a clinical diagnosis of autoimmune cholestasis. Dig Dis Sci 2004;49:1957-1961.
[51] Cotrim HP, Andrade ZA, Parana R, Portugal M, Lyra LG, Freitas LA. Nonalcoholic steatohepatitis: a toxic liver disease in industrial workers. Liver 1999;19:299-304.
[52] De Luca-Johnson J, Wangensteen KJ, Hanson J, Krawitt E, Wilcox R. Natural History of Patients Presenting with Autoimmune Hepatitis and Coincident Nonalcoholic Fatty Liver Disease. Dig Dis Sci 2016;61:2710-2720.

[53] Choi HS, Brouwer WP, Zanjir WM, de Man RA, Feld JJ, Hansen BE, et al. Non-Alcoholic steatohepatitis is associated with liver-related outcomes and all-cause mortality in chronic hepatitis B. Hepatology 2019.
[54] Chiang DJ, McCullough AJ. The Impact of Obesity and Metabolic Syndrome on Alcoholic Liver Disease. Clin Liver Dis 2014;18:157-+.
[55] Ajmera VH, Terrault NA, Harrison SA. Is Moderate Alcohol Use in Nonalcoholic Fatty Liver Disease Good or Bad? A Critical Review. Hepatology 2017;65:2090-2099.
[56] Ceballos N, Babor TF. Editor's Corner: Binge Drinking and the Evolving Language of Alcohol Research. J Stud Alcohol Drugs 2017;78:488-490.
[57] Cespiati A, Youngson NA, Tourna A, Valenti L. Genetics and Epigenetics in the Clinic: Precision Medicine in the Management of Fatty Liver Disease. Curr Pharm Des 2020.
[58] Eslam M, George J. Genetic contributions to NAFLD: leveraging shared genetics to uncover systems biology. Nat Rev Gastroenterol Hepatol 2019.
[59] Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: Clinical impact. Journal of Hepatology 2018;68:268-279.
[60] Fracanzani AL, Petta S, Lombardi R, Pisano G, Russello M, Consonni D, et al. Liver and Cardiovascular Damage in Patients With Lean Nonalcoholic Fatty Liver Disease, and Association With Visceral Obesity. Clin Gastroenterol H 2017;15:1604-+.
[61] Hulley SB. Designing clinical research: Lippincott Williams & Wilkins; 2007.
[62] Alcohol Facts and Statistics; In: Alcoholism NIoAAa, editor. . 2017.

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Hepatic steatosis in adults

(detected either by imaging techniques, blood biomarkers/scores or by liver histology)

Overweight or obesity

(defined as BMI ≥25 kg/m^2 in Caucasians or BMI ≥23 kg/m^2 in Asians)

Lean/normal weight

(defined as BMI <25 kg/m^2 in Caucasians or BMI <23 kg/m^2 in Asians)

Type 2 diabetes mellitus

(According to widely accepted international criteria)

If presence of <u>at least</u> two metabolic risk abnormalities:

- Waist circumference ≥102/88 cm in Caucasian men and women (or ≥90/80 cm in Asian men and women).
- Blood pressure ≥130/85 mmHg or specific drug treatment.
- Plasma triglycerides ≥150 mg/dL (≥1.70 mmol/l) or specific drug treatment .
- Plasma HDL-cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment.
- Prediabetes (i.e., fasting glucose levels 100 to 125 mg/dL (5.6 to 6.9 mmol/L), or 2-hour post-load glucose levels 140 to 199 mg/dL (7.8 to 11.0 mmol) or HbA1c 5.7% to 6.4% (39–47 mmol/mol)).
- Homeostasis model assessment (HOMA)-insulin resistance score ≥2.5
- Plasma high-sensitivity C-reactive protein (hs-CRP) level >2 mg/L

MAFLD

(Metabolic associated fatty liver disease)