Expert Opinion

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A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement

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Summary

The exclusion of other chronic liver diseases including "excess" alcohol intake has until 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 for the diagnosis of MAFLD that is both comprehensive and simple, 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 *vs.* 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.

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 calorie intake relative to expenditure in nutritionally imbalanced and unhealthy diets.[4] In parallel, the prevalence of poor metabolic health in adults from affluent countries is high, even in normal weight individuals.[5,6] In this context of high risk and prevalence, the lack of 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 dysfunction-associated fatty liver disease, MAFLD, has been proposed as a more appropriate term to describe the liver disease associated with 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 so 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 ICD systems and diagnosis-related groups. 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]

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 Box 1. A flowchart for the proposed diagnostic criteria is depicted in Fig. 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 of <20%, and its performance is suboptimal in individuals with body mass index (BMI) >40 kg/m^2. Measurement of controlled attenuation parameter (or similar) using vibration-controlled transient elastography (FibroScan) is increasingly undertaken in routine clinical practice, with a reported area under the area under the receiver-operating-characteristic curve of 0.87 for steatosis, using biopsy as the reference standard.[19] CT or MRI can be used to diagnose moderate and severe steatosis if available. Magnetic resonance spectroscopy (MRS) provides a quantitative estimation of liver fat, but it is expensive, has limited availability, and requires special software. Therefore, MRI-derived proton density fat fraction 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 the available data on 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 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 (Fig. 1) stems from the fact that it has strong pathological link to MAFLD and 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 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[22,23] with purported differential impacts on the 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 individuals with MHO and MAFLD remain at high risk of developing significant hepatic fibrosis.[27] Thus, the presence of both excess weight and metabolic dysfunction have independent effects on the 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 T2DM has been demonstrated; >70% of patients with T2DM have MAFLD.[28,29] This criterion can also be applied in clinical practice (Fig. 1).

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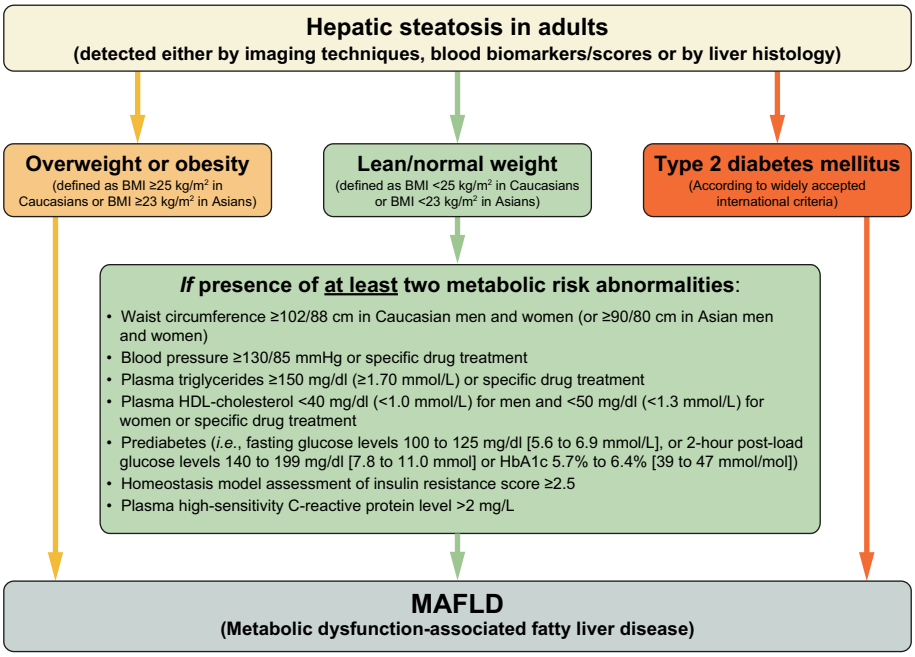

Fig. 1. Flowchart for the proposed "positive" diagnostic criteria for MAFLD.

In addition, the presence of steatosis with at least two metabolic risk abnormalities mentioned in Box 1 and Fig. 1 should be a criterion to diagnose MAFLD in non-overweight/obese individuals. 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.[2,30] Indeed, in a recent study of 1,000 liver biopsies in patients with MAFLD, the histological severity of disease in patients with a BMI <23 kg/m^2 was no different to that in those with a BMI >25 kg/m^2.[31] There is also growing evidence that the importance of metabolic health extends 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 need to be considered.[32] Some studies suggest that liver fat accumulation is a very sensitive and early indicator of metabolic dysfunction.[33,34] 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 used to describe the disease. Disease severity would 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.[35] 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.[36] Beyond this qualitative association, several longitudinal studies, both natural history-based and interventional, have demonstrated a semi-quantitative 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 the persistence of steatohepatitis.[37–40] Pharmacological interventions and long-term observational natural history studies have shown the same directionality between activity grade, hepatic inflammatory changes and fibrosis progression/regression.[39,41]

The aforementioned findings suggest that a dichotomous classification to non-alcoholic steatohepatitis (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 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.[42]

From a clinical and pathological concept, this suggestion should result in improved case identification, while subclassification 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 categorisation possible; liver biopsy should be reserved for complicated cases, where it may be needed to rule out other forms of liver disease, or to further characterise the disease process, as the pathology score represents not only "amount" but also location and parenchymal alteration, *e.g.* vascular alterations.

Box 1. Criteria defining metabolic risk factors.

Increased cardiometabolic and MAFLD risk defined as the presence of at least two of the following 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 to 47 mmol/mol])
- Homeostasis model assessment of insulin resistance score ≥2.5
- Plasma high-sensitivity C-reactive protein level >2 mg/L

*The AHA/NHLBI guidelines for metabolic syndrome recognise 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). HbA1c, glycated haemoglobin; MAFLD, metabolic dysfunction-associated fatty liver disease.

Box 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 Box 1, with at least one of the following:

i) Documentation of MAFLD on a previous liver biopsy*.

ii) 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. MAFLD, metabolic dysfunction-associated fatty liver disease.

MAFLD cirrhosis—no longer cryptogenic cirrhosis

Suggestion

We propose that patients with cirrhosis, with low or undetectable levels of steatosis, 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 (Box 1) with at least one of the following i) documentation of MAFLD on a previous liver biopsy, ii) historical documentation of steatosis by hepatic imaging (Box 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.[43–45] 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,[46] viral infections (HIV, HBV or HCV), drug-induced liver injury, autoimmune hepatitis either at baseline or at follow-up is not a prerequisite 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[47] (Box 3).

Rationale

With the dramatic rise in the global prevalence of MAFLD, it can and frequently does coexist with

Box. 3. Dual aetiology fatty liver disease (concomitant MAFLD and other liver disease).

Meeting the criteria for a diagnosis of MAFLD

Plus

Any other cause of 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, drug-induced liver injury 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. MAFLD, metabolic dysfunction-associated fatty liver disease.

other conditions such as viral hepatitis and ALD.[48–50] These individuals likely have a different natural history and response to therapy[51–53] than those with liver disease of a single aetiology. Moreover, the currently recommended cut-offs to define significant alcohol consumption, or the duration of alcohol withdrawal that constitutes abstinence, in those with suspected MAFLD are arbitrary.[54] 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[55] 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 interviews will aid in diagnosis but will not be required, as dual aetiology fatty liver disease is possible and even frequent.[47]

Disease subphenotyping

MAFLD may, in the future, be subclassified 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 subclassification will be particularly valuable for MAFLD given its substantial heterogeneity.[56–58] Thus, while we suggest the umbrella term MAFLD, it is in the knowledge that further subclassification will likely ensue. Subclassification 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.[1,57]

A likely consequence of implementing the proposed diagnostic criteria for MAFLD will be to highlight a new category of fatty liver disease, including a relative minority of patients previously deemed as affected by NAFLD that is not MAFLD, and cannot be attributed to alcohol or other known causes.[30,59] 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 "alternative 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, 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. The term "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 regarding their intended purpose (Table S1). 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. By contrast, inclusion criteria for trials or studies are the main attributes of a study target population that the investigators will utilise to address their research question.[60] The differences between diagnostic and inclusion criteria will depend on a variety of factors, including the study or trial design, as well as drugs' specific mechanisms of action, but not necessarily on clinical features of 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 also included 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, potentially with 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, hepatology faces unique challenges in discriminating between pure alcohol-associated and pure metabolic dysfunction-associated disorders with similar manifestations and overlapping features. Lessons can be learned from the viral hepatitis field, with direct-acting antivirals leading to revolutionary changes such that clinical trials moved to explore the benefit of therapy in HIV/HCV-coinfected 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 coexist with other conditions (Fig. 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 subphenotype 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.

Abbreviations

ALD, alcohol-associated fatty liver disease; BMI, body mass index; FLI, fatty liver index; HbA1c, glycated haemoglobin; MAFLD, metabolic dysfunction-associated fatty liver disease; MHO, metabolically healthy obesity; MRS, magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

ME, PNM, SKS, QMS,GT, MRG, SZS, VWS, JFD, JS,TK, MA, LV, GS, CT, HYJ, JGF,HG, YY, HCP, CPO,PB,

LA,MHZ,YF,WKC, NMS, SHA, LC, EB, VR, JG, contributed to conceptualisation and the writing of the manuscript.

Supplementary data

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Author names in bold designate shared co-first authorship

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