Nonalcoholic fatty liver disease: an update

Giorgio Bedogni[a,b], *Francesco Palmese*[a,b] *and Francesco Giuseppe Foschi*[c]

Purpose of review
We discuss two recent controversial issues in the research field of fatty liver: the proposal to replace nonalcoholic fatty liver disease (NAFLD) with metabolically associated fatty liver disease (MAFLD) and the suggestion to extend to primary care the noninvasive testing for liver fibrosis that was developed for secondary care.

Recent findings
There is preliminary evidence that MAFLD-only patients are at greater risk of fibrosis than NAFLD-only patients. There are a large number of false positives associated with the downshift of noninvasive testing for liver fibrosis from secondary to primary care.

Summary
More studies are needed to compare the MAFLD and NAFLD operational definitions. Noninvasive testing of liver fibrosis also needs further evaluation before it can be used in primary care or in the general population.

Keywords
diagnostic downshift, epidemiology, liver fibrosis, metabolically associated fatty liver disease, nonalcoholic fatty liver disease

INTRODUCTION

We discuss two recent controversial issues in the research field of fatty liver: the proposal to replace nonalcoholic fatty liver disease (NAFLD) with metabolically associated fatty liver disease (MAFLD) and the suggestion to extend to primary care the noninvasive testing for liver fibrosis that was developed for secondary care.

THE NONALCOHOLIC FATTY LIVER DISEASE VS. METABOLICALLY ASSOCIATED FATTY LIVER DISEASE CONTROVERSY

The most debated topic in the research field of fatty liver is whether the recently introduced concept of metabolic dysfunction-associated fatty liver disease (MAFLD) should replace the old and time-tested concept of NAFLD [1,2▪,3▪,4,5].

When we say that the NAFLD concept is time-tested, we do not wish to deny its limitations, which we have repeatedly emphasized in our work [6], but simply to point out that the large evidence base built around the 'old' diagnostic category of NAFLD may not be transferrable to the 'new' diagnostic category of MAFLD [3▪,5]. We will not have a problem with considering the available research on NAFLD as a 'sunk cost', if MAFLD is shown to be better than NAFLD because this is how science works and having 'skin in the game' is a central part of the scientific enterprise [7]. However, we believe that we are not there as yet, although we, of course, will welcome any advancement in the field and will try to actively contribute to it.

NAFLD is operationally defined as the presence of steatosis in more than 5% of hepatocytes in the absence of significant alcohol consumption and other causes of liver disease [8]. As reported by Eslam *et al.* [2▪], it is the negative nature of the NAFLD definition to have prompted the positive one of MAFLD (Table 1). In the view of its proponents, such positive definition is an advantage over the negative definition of NAFLD. However, NAFLD supporters can reasonably object that, albeit it is

[a]Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, [b]Department of Primary Healthcare, Internal Medicine Unit addressed to Frailty and Aging, S. Maria delle Croci Hospital, AUSL Romagna, Ravenna and [c]Department of Internal Medicine, Degli Infermi Hospital, AUSL Romagna, Faenza, Italy

Correspondence to Dr Giorgio Bedogni, Department of Primary Healthcare, Internal Medicine Unit addressed to Frailty and Aging, Santa Maria delle Croci Hospital, AUSL Romagna, Viale Randi 5, 48121 Ravenna, Italy. Tel: +39 0544 285273; e-mail: giorgio.bedogni@unibo.it

Curr Opin Lipidol 2023, 34:000–000
DOI:10.1097/MOL.0000000000000874

KEY POINTS

- A new concept of metabolically associated fatty liver disease has been proposed to replace that of nonalcoholic fatty liver disease.
- Although this proposal has been endorsed with enthusiasm by most researchers, there is a need for more studies comparing the relative merits of MAFLD and NAFLD.
- Increased number of false-positive referrals could be caused by the shifting of noninvasive tests of liver fibrosis from secondary to primary care.

psychologically better to tell what an entity is rather than what it is not, this practice is commonplace in Medicine and cannot be considered a scientific advancement [3▪,4]. A potential advantage of the MAFLD over the NAFLD definition is nonetheless the fact that MAFLD allows a diagnosis of dual-etiology fatty liver disease [2▪] (Table 2).

Table 1. Operational definition of metabolic dysfunction associated fatty liver disease (MAFLD) in adults

Hepatic steatosis AND (overweight or obesity OR type 2 diabetes mellitus OR normal weight with at least two metabolic abnormalities)
Where:
Hepatic steatosis can be detected by imaging techniques, blood biomarkers or liver histology.
Overweight is defined as BMI at least 25 kg/m^2 in Caucasians or at least 23 kg/m^2 in Asians.
Normal weight is defined as BMI less than 25 kg/m^2 in Caucasians and less than 23 kg/m^2 in Asians
Metabolic abnormalities are defined as follows:
1. Waist circumference at least 102/88 cm in Caucasian men and women or at least 90/80 cm in Asian men and women[a];
2. Blood pressure at least 130/85 mmHg or specific drug treatment;
3. Triglycerides at least 150 mg/dl or specific drug treatment;
4. HDL-cholesterol less than 40 mg/dl for men and less than 50 mg/dl for women or specific drug treatment;
5. Prediabetes as defined by
5a. Fasting glucose from 100 to 125 mg/dl or
5b. 2 h postload glucose from 140 to 199 mg/dl or
5c. HbA1c from 5.7 to 6.4%;
6. Homeostasis model assessment of insulin resistance (HOMA-IR) at least 2.5;
7. Plasma high-sensitivity C-reactive protein level (hs-CRP) greater than 2 mg/l.

[a]The US guidelines suggest different cut-points for waist circumference, that is, at least 94/80 cm in Caucasian men and women.

Table 2. Diagnosis of dual etiology fatty liver disease

Metabolic dysfunction associated fatty liver disease (MAFLD) AND any other cause of liver disease, for example,
alcohol-use disorder defined as consumption of >3 drinks per day in men and >2 drinks per day in women;
binge drinking (defined as >5 drinks in males and >4 drinks in females, consumed over a 2-h period);
viral infection (HIV, HBV and HCV);
autoimmune hepatitis;
inherited liver disorders;
drug-induced liver injury;
other known liver disease.

The metabolic abnormalities listed as 1, 2, 3, 4 and 5 in Table 1 can be easily recognized as the components of the metabolic syndrome [9]. In this respect, it is fair to notice that, despite the enormous success of the concept and the nearly universal adoption of the diagnosis of metabolic syndrome, the clinical relevance of this concept is still debated because the risk of cardiometabolic disease associated with the syndrome does not exceed that associated with its single components [10]. Furthermore, even if fatty liver continues to be considered the hepatic manifestation of the metabolic syndrome by many researchers and clinicians, this is increasingly controversial, because of the heterogeneity not only of the metabolic syndrome but also of fatty liver [3▪,5].

The metabolic abnormalities listed as 6 and 7 in Table 1, that is, the homeostasis model assessment of insulin resistance (HOMA-IR), calculated from fasting glucose and insulin, and high-sensitivity C-reactive protein (hs-CRP), will require an extension of the examinations hitherto performed to diagnose fatty liver, at least outside specialty centers. They will also make it difficult to reuse data from existing population studies of fatty liver where HOMA-IR and/or hs-CRP were not measured, unless one accepts that the definition of MAFLD is not satisfied in its entirety. For instance, hs-CRP was not available as diagnostic criterion for MAFLD in a recent cross-sectional analysis of the Rotterdam study aimed at establishing the association of MAFLD with liver fibrosis using liver stiffness as the diagnostic method [11]. Many other available and ongoing studies are likely to suffer from this problem, including our Dionysos and Bagnacavallo studies, for which hs-CRP measurements are not available [6]. In our opinion, simulation studies performed within existing or future cross-sections and cohorts with availability of all diagnostic

criteria for MAFLD will be central to understand whether the experimentally induced missingness of one or more diagnostic criteria for MAFLD can impact study outcomes [12].

As even a cursory glance at PubMed will show, hundreds of articles have endorsed the new definition of MAFLD in the past 2 years – continuing the trend of increasing popularity met by fatty liver in general and by NAFLD, in particular. However, most of these articles do not shed light on the relative merits of the two operational definitions. What is needed are – at least – studies comparing NAFLD and MAFLD for their ability to predict clinically relevant outcomes. Such studies can be classified under the rubric of prognostic modeling, always taking into account the fact that a risk factor is not a prognostic factor and neither of them is an etiological factor until proven so [13]. Another important warning is that, in order to figure out the true value of a potential prognostic factor, known risk factors for the given outcome should be taken into account. This is not easy as it may seem as it implies a very reasoned choice of models and metrics of effects size [6,12,13].

Studies comparing the NAFLD and MAFLD operational definitions are becoming increasingly available and metanalyses of them are starting to appear [14▪▪], even with the limitations inherent to the heterogeneity of the underlying primary studies, that is, the different case-mix of patients, the different criteria used to diagnose fatty liver and other liver disease, and the different distributions of known steatogenic agents, for example, alcohol, drugs and HCV infection. Not unexpectedly, most cases of MAFLD and NAFLD overlap [11,14▪▪] – with MAFLD normally counting more cases of fatty liver than NAFLD – and this has led to the suggestion that it is better to evaluate and compare the nonoverlapping NAFLD-only and MAFLD-only groups rather than the overlapping MAFLD and NAFLD groups [11,14▪▪,15]. In this regard, a recent metanalysis estimated the relative risk of fibrosis to be 4.2 [95% confidence interval 1.3–12.9] in MAFLD-only vs. NAFLD-only patients [14▪▪]. The separation of NAFLD-only and MAFLD-only patients is certainly a good suggestion, especially at the present stage of research, but it incurs in a great loss of data available for inference, which could perhaps be avoided by building multivariable regression models having the binary components of NAFLD and MAFLD as predictors so that their relative contribution to the outcome of interest can be formally weighted [6]. (Of course, albeit sometimes useful in practice, the dichotomization of continuous outcomes is known to induce by itself substantial loss of information [16].) It is presently unknown, for instance, whether a person with a diagnosis of MAFLD because of the association of fatty liver with type 2 diabetes mellitus has the same risk of liver cirrhosis as a person with a diagnosis of MAFLD because of fatty liver and normal weight, high triglycerides, and low-HDL cholesterol (Table 1). A similar problem occurs with the definition of the metabolic syndrome, where each component is equally weighted for the purpose of diagnosis [17]. Importantly, it is likely that metanalyses will be needed to pool data from different studies to get precise estimates of effect sizes because the MAFLD-only and NAFLD-only categories are uncommon [14▪▪]. Moreover, the same concept of MAFLD is likely to undergo further revision on the basis of the expanding evidence base [11,14▪▪,15] as it was predicted by its promoters [2▪].

As we pointed out at the opening of this article and other researchers have discussed at length [5], the most relevant issue inherent with the choice of MAFLD over NAFLD is that the clinically relevant research produced for NAFLD may not be transferrable to MAFLD. For instance, a recent and important study of all adults diagnosed with NAFLD between 1996 and 2016 in Olmsted County (Minnesota, USA) evaluated the time and risk of progression from NAFLD to cirrhosis to decompensation and death and provided data to understand the natural history of NAFLD and to inform the design of clinical trials [18▪▪]. There was a small proportion of people who had liver-related outcomes in this population-based cohort with a median follow-up of 23 years. This led to the conclusion that large sample sizes and long follow-up are required to detect reductions in liver-related endpoints in clinical trials of NAFLD. Another recent and important cohort study followed up all individuals with biopsy-proven NAFLD diagnosed in Sweden from 1966 to 2017 for a mean follow-up time of 16.6 years [19▪▪]. There was significant excess mortality risk found across all histopathological stages of NAFLD, including simple steatosis, and it increased with worsening NAFLD severity. The increased risk was because of deaths from extrahepatic cancer and cirrhosis, while the contributions of cardiovascular disease and hepatocellular carcinoma were relatively modest. Whether these and other important findings reported for NAFLD can be transferred to the new diagnostic category of MAFLD is unknown, even if this seems unlikely because of the weight given by MAFLD to the components of the metabolic syndrome [3▪,5].

THE DIAGNOSTIC DOWNSHIFT OF NONINVASIVE TESTING FOR LIVER FIBROSIS

The clinical relevance of NAFLD as liver-related outcomes are concerned stems mostly from its

association with liver fibrosis [6,8]. The reference method for the diagnosis of liver fibrosis is liver biopsy, which cannot be performed outside specialty centers and, of course, in the general population. The true prevalence of liver fibrosis in the general population is, therefore, presently unknown.

The available noninvasive methods for the assessment of liver fibrosis, such as the measurement of liver stiffness and noninvasive markers, have been cross-validated against liver biopsy in secondary care centers [6]. The calculation of the most commonly employed noninvasive markers of liver fibrosis is detailed in Table 3. FIB-4 is the most common of these markers, as it requires measurements performed almost routinely in primary care or epidemiological studies (age, aspartate transaminase and platelets).

Most epidemiological studies of liver fibrosis performed in primary care or in the general population employ the same cut-off values of liver stiffness or noninvasive markers developed for patients followed at specialty centers. In addition, practice guidelines for the diagnosis of liver fibrosis are increasingly recommending the adoption in secondary care of cut-points developed for primary care [20].

This so-called 'diagnostic downshift', which extrapolates secondary care testing tactics to primary care, is expected to result in unintended consequences [21▪▪]. Even tests with near 100% specificity are expected to have a substantial number of false-positive findings in low prevalence settings.

Table 3. Calculation of the main noninvasive indexes of fibrosis

AST/ALT ratio = ast/alt
APRI (AST to platelet ratio index) = (ast/astuln)/plt
GGT = ggt
FIB-4 = age∗ast/plt∗sqrt(alt)
BARD = 1[a] if BMI ≥ 28 + 2[a] if astalt ≥ 0.8 + 1[a] if diabetes
FORNS INDEX = 7.811 − 3.131∗ln(plt) + 0.781∗ln(ggt) + 3.467∗ln(age) − 0.014∗ch
BAAT = 1[a] if age ≥ 50 + 1[a] if bmi ≥ 28 + 1[a] if tg ≥ 1.7 + 1[a] if alt ≥ 2∗altunl
NFS (NAFLD fibrosis score) = −1.675 + 0.037∗age + 0.094∗bmi + 1.13 if ifg OR diabetes[a] + 0.99∗astalt − 0.013∗plt − 0.66∗alb

[a]0 if otherwise.
Where: age, age (years); alb, albumin (g/l); alt, alanine transaminase (U/l); altunl, upper normal limit of alanine transaminase (U/l); ast, aspartate transaminase (U/l); astalt, AST (U/l)/ALT (U/l); astuln, upper normal limit of aspartate transaminase (U/l); ch, cholesterol (mg/dl); diabetes, diabetes mellitus (presence of); ggt, gamma-glutamyl-transferase (U/l); ifg, impaired fasting glucose (presence of); ln, natural logarithm; plt, platelets (10^9/l); sqrt, square root; tg, triglycerides (mmol/l).

Even if the prevalence of liver fibrosis in the primary care population is presently unknown, it is certainly lower than that reported in the secondary care population [6]. Under the assumption that the specificity (true negative fraction) – which is higher than the sensitivity (true positive fraction) – of noninvasive markers of fibrosis will be the same in primary care as in secondary care, an excess of false-positive cases can be expected in primary care because of the lower prevalence of fibrosis.

We have recently used data from the Bagnacavallo study to evaluate the continuous association between liver stiffness and the most common noninvasive markers of liver fibrosis [22]. We found that the mean change in liver stiffness measured by transient elastography associated with an increase from the 5th to the 95th internal percentile of widely employed noninvasive indexes of fibrosis (AST/ALT ratio, APRI, Forns index, FIB-4, GGT, BARD and BAAT) was low and of doubtful clinical relevance. These findings raise doubts about the ability of such markers to diagnose liver fibrosis in the general population.

Other researchers have recently demonstrated a lack of association between noninvasive indexes (FIB-4, APRI) and liver stiffness measured by transient elastography in a subsample of individuals from the general population deemed to be at high risk of NAFLD [23]. Even more importantly for its practical implications, a recent study of five populations in Spain, Hong Kong, Denmark, England and France has shown that there is about a third of false positive results when FIB-4 and NFS are used at conventional cut-points to diagnose liver fibrosis as compared with liver stiffness as diagnosed by transient elastography again at conventional cut-points [24].

CONCLUSION

The concept of MAFLD has gained popularity in the past 2 years, but the decision on whether it can replace NAFLD in everyday practice needs to be carefully evaluated. Because of the phenomenon of 'diagnostic downshift', caution should be taken when applying noninvasive testing for liver fibrosis developed in secondary care.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020; 158:1999.e1–2014.e1.
2. ■ Eslam M, Newsome PN, Sarin SK, *et al.* A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020; 73:202–209.

The new definition of metabolically associated fatty liver disease.

3. ■ Singh SP, Anirvan P, Reddy KR, *et al.* Nonalcoholic fatty liver disease: not time for an obituary just yet. J Hepatol 2021; 74:972–974.

The main objections to the proposal of replacing nonalcoholic fatty liver disease with metabolically associated fatty liver disease.

4. Younossi ZM, Rinella ME, Sanyal AJ, *et al.* From NAFLD to MAFLD: implications of a premature change in terminology. Hepatology 2021; 73:1194–1198.
5. Singh SP, Anirvan P, Khandelwal R, Satapathy SK. Nonalcoholic fatty liver disease (NAFLD) name change: Requiem or Reveille. J Clin Translat Hepatol 2021; 9:931–938.
6. Bedogni G, Gastaldelli A, Foschi FG. Fatty liver, cardiometabolic disease and mortality. Curr Opin Lipidol 2020; 31:27–31.
7. Mayo DG. Statistical Inference as severe testing. Cambridge: Cambridge University Press; 2018.
8. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL–EASD–EASO Clinical Practice Guidelines for the management of nonalcoholic fatty liver disease. J Hepatol 2016; 64:1388–1402.
9. Alberti KG, Eckel RH, Grundy SM, *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.
10. Nilsson PM, Tuomilehto J, Rydén L. The metabolic syndrome - what is it and how should it be managed. Eur J Prev Cardiol 2019; 26:33–46.
11. van Kleef LA, Ayada I, Alferink LJM, *et al.* Metabolic dysfunction-associated fatty liver disease improves detection of high liver stiffness: the Rotterdam Study. Hepatology 2022; 75:419–429.
12. Harrell F. Regression modeling strategies. Switzerland: Springer: Cham; 2016.
13. Riley RD, Van der Windt D, Croft P, Moons KGM. Prognosis research in healthcare. Oxford: Oxford University Press; 2019.
14. ■■ Ayada I, van Kleef LA, Alferink LJM, *et al.* Systematically comparing epidemiological and clinical features of MAFLD and NAFLD by meta-analysis: focusing on the nonoverlap groups. Liver Int 2022; 42:277–287.

Meta-analysis comparing MAFLD-only with NAFLD-only patients in order to establish different clinical features and prognostic implications.

15. van Kleef LA, de Knegt RJ. The transition from NAFLD to MAFLD: One size still does not fit all-Time for a tailored approach. Hepatology 2022; 76:1243–1245.
16. Greenland S. Invited commentary: the need for cognitive science in methodology. Am J Epidemiol 2017; 186:639–645.
17. Ferrannini E. Metabolic syndrome: a solution in search of a problem. J Clin Endocrinol Metab 2007; 92:396–398.
18. ■■ Allen AM, Therneau TM, Ahmed OT, *et al.* Clinical course of nonalcoholic fatty liver disease and the implications for clinical trial design. J Hepatol 2022; 77:1237–1245.

A very important contribution to the understanding of the progression of NAFLD in the general population with implications for the design of clinical trials.

19. ■■ Simon TG, Roelstraete B, Khalili H, *et al.* Mortality in biopsy-confirmed nonalcoholic fatty liver disease: results from a nationwide cohort. Gut 2021; 70:1375–1382.

A very important contribution to the understanding of the progression of NAFLD in patients who have undergone liver biopsy. Although these patients cannot be compared to individuals from the general population, an important finding of this study is that excess mortality risk is found across all histopathological stages of NAFLD. This goes against the available evidence obtained by most of the available case series.

20. Jacobson IM, Wong VW, Castera L, *et al.* Expert panel consensus on clinical assertion statements describing noninvasive tools for diagnosing nonalcoholic steatohepatitis. J Clin Gastroenterol 2022; doi: 10.1097/MCG.0000000000001780. [Online ahead of print]
21. ■■ Sajid IM, Frost K, Paul AK. 'Diagnostic downshift': clinical and system consequences of extrapolating secondary care testing tactics to primary care. BMJ Evid Based Med 2022; 27:141–148.

An excellent description of the phenomenon of diagnostic downshift and of its pervasiveness in almost all fields of medicine.

22. Foschi FG, Domenicali M, Giacomoni P, *et al.* Is there an association between commonly employed biomarkers of liver fibrosis and liver stiffness in the general population. Ann Hepatol 2020; 19:380–387.
23. van Dijk AM, Vali Y, Mak AL, *et al.* Noninvasive tests for nonalcoholic fatty liver disease in a multiethnic population: the HELIUS study. Hepatol Commun 2022.
24. Graupera I, Thiele M, Serra-Burriel M, *et al.* Low accuracy of FIB-4 and NAFLD fibrosis scores for screening for liver fibrosis in the population. Clin Gastroenterol Hepatol 2022; 20:2567.e6–2576.e6.