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EDITORIAL

The transition from NAFLD to MAFLD: One size still does not fit all—Time for a tailored approach?

The publication of the novel MAFLD criteria has caused a lot of controversy and was the start of a scientific contest between NAFLD and MAFLD. To date, over 1,000 articles cited the novel criteria, indicating the widespread attention.

Before we can focus on any of the arguments for or against the transition, it is important to realize the differences between the proposed MAFLD definition and the conventional NAFLD definition (Figure 1).[1,2] For the presence of NAFLD, secondary causes for steatosis must be ruled out. Depending on the geographical region, this will predominantly be excessive alcohol consumption and/or viral hepatitis, but it can also be steatogenic drug use or the presence of other liver diseases. In contrast, for MAFLD, secondary causes of steatosis are no longer exclusion criteria, but the presence of metabolic dysfunction is required. These different definitions result in the following mutually exclusive groups: MAFLD+/NAFLD+, MAFLD−/NAFLD+, MAFLD+/NAFLD−, and MAFLD−/NAFLD−.

The debate on which definition to use focuses on the nonoverlapping groups MAFLD−/NAFLD+ and MAFLD+/NAFLD−. As a result of the different definitions, MAFLD−/NAFLD+ is characterized by steatosis in the absence of metabolic dysfunction and secondary causes for steatosis. MAFLD+/NAFLD−, on the other hand, is characterized by the simultaneous presence of steatosis, metabolic dysfunction, and excessive alcohol consumption or viral hepatitis. Thus, individuals with MAFLD+/NAFLD− have, by definition, additional risk factors for advanced liver disease.

In this issue of *Hepatology,* Younossi and colleagues importantly contributed to the ongoing debate by reporting on the long-term outcomes in patients with NAFLD and MAFLD.[3] They used the well-defined NHANES cohort together with restricted mortality files to provide a comprehensive overview of all-cause and cause-specific mortality in the general population of the United States. During the 23 years median follow-up, 30% of the 12,878 participants died, providing a solid base for investigating causes of mortality in patients with NAFLD and MAFLD. First, they report a very high correlation between NAFLD and MAFLD (kappa, 0.83–0.94), similar to a recent meta-analysis showing ±80% had both NAFLD and MAFLD, ±15% only MAFLD, and ±5% only NAFLD.[4]

The authors were the first to investigate a range of clinically relevant predictors for all-cause and cause-specific mortality in patients with NAFLD and MAFLD. Driven by the large overlap between NAFLD and MAFLD, no differences were observed in risk factors for all-cause mortality despite slight changes in effect size. However, interestingly, the authors reported 70 liver-related deaths in patients with fatty liver disease. This is quite a large number, especially for general population cohorts after excluding viral hepatitis. Of these 70 deaths, 23 occurred in individuals with alcoholic liver disease (ALD [and thus, MAFLD+/NAFLD−]); the remaining liver deaths ($n = 47$) all occurred in patients with MAFLD+/NAFLD+, and no liver deaths were reported in individuals with MAFLD−/NAFLD+. FIB-4 ≥2.67, indicating a high risk for fibrosis, was the main predictor for liver-related mortality in both patients with MAFLD (HR, 17.2) and patients with NAFLD (HR, 9.3), aligning with previous studies indicating that fibrosis is the main predictor for adverse outcomes in patients with NAFLD.[5] Additionally, in patients with MAFLD, ALD (HR, 4.5) was a significant risk factor for liver-related mortality, whereas in patients with NAFLD, high C-reactive protein (HR, 4.5) and insulin resistance (HR, 3.6) were crucial predictors. The finding that insulin resistance is only a risk factor for liver-related mortality in patients with NAFLD is remarkable. ALD, however, might obscure other risk factors and, therefore, the conclusion that NAFLD better captures the metabolic effects on mortality as compared with MAFLD may be premature. After all, almost 50% more liver-related deaths were reported in patients with MAFLD than in patients with NAFLD. All these additional deaths occurred in patients with ALD, in which the presence of MAFLD could have contributed to disease progression but may not be the primary driver. Hence, characteristics and predictors

Abbreviations: ALD, alcoholic liver disease; MAFLD, metabolic dysfunction associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NHANES, National Health and Nutrition Examination Survey.

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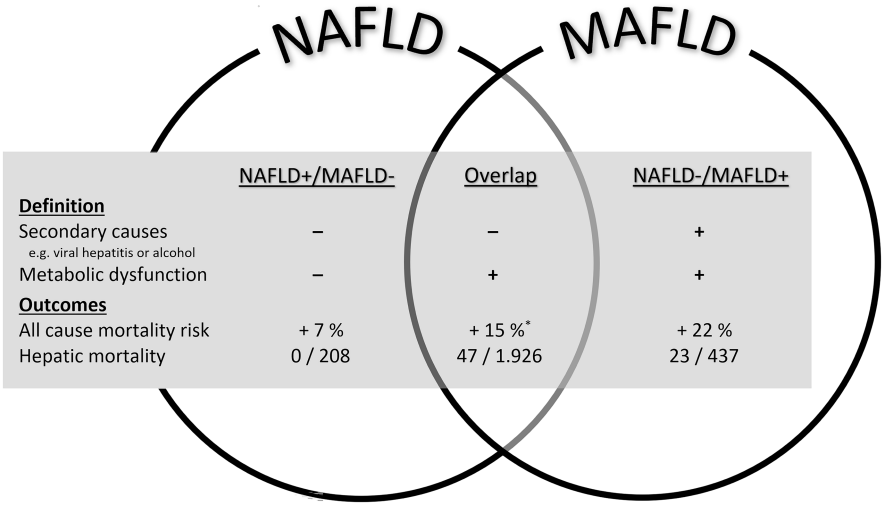

FIGURE 1 An overview of the differences in the definition and outcomes for the mutually exclusive groups. All-cause mortality risk was compared to NAFLD−/MAFLD− and only the result in the overlap (NAFLD+/MAFLD+) reached statistical significance.

for mortality may differ from the more homogenous NAFLD group.

The authors demonstrated that NAFLD and MAFLD were not associated with mortality in fully adjusted models. From this starting position, it may be challenging to use mortality as a marker for the NAFLD and MAFLD definition performance. Nonetheless, when focusing on the mutually exclusive groups, patients with MAFLD+/NAFLD+ were at a significantly increased mortality risk (HR, 1.15) compared with individuals without fatty liver disease. Hence, the authors concluded that it was not MAFLD, but metabolic dysfunction in patients with NAFLD that increased mortality risk. However, similar mortality risk was observed while focusing on the MAFLD+/NAFLD− group (HR, 1.22). Although this was indeed not significant—probably because of small numbers and relatively small effect size—we believe this suggests an equally harmful effect in the MAFLD+/NALFD− group in fully adjusted models and does not rule out excess mortality because of MAFLD in individuals with ALD.

As became clear from this elegant study, the role of alcohol intake in MAFLD is complicated. Additional adjusting for ALD resulted in MAFLD no longer being a significant risk factor for mortality. It was suggested that ALD was a mediator in the association between MAFLD and mortality. Rather than the authors' suggestion of mediation, we believe alcohol consumption might be (besides an individual predictor for mortality) a moderator potentially facilitating synergistic risk. To decompose the effects of alcohol in patients with MAFLD on mortality, we recommend a careful extensive assessment of all groups (MAFLD+/ALD+, MAFLD−/ALD+, MAFLD+/ALD−, and MAFLD−/ALD−). Only with this approach, one can conclude whether the prognosis of patients with MAFLD and ALD is solely dependent on their alcohol consumption (equal risk in MAFLD+/ALD+ and MAFLD−/ALD+), or also on the presence of MAFLD (higher risk of MAFLD+/ALD+ than MAFLD−/ALD+), or whether there is a synergistic risk (MAFLD+/ALD+ at higher risk than the product of MAFLD+/ALD− and MAFLD−/ALD+). Although MAFLD in patients with chronic hepatitis B has already been shown to be an independent risk factor for adverse outcomes,[6] this method might also be useful in further decomposing the effects of viral hepatitis (and less prevalent secondary causes of steatosis) on the outcomes of patients with MAFLD. We are looking forward to studies using these methods to shed further light on the complex interactions of concomitant liver diseases in patients with MAFLD.

A clear answer is warranted on whether it is safe to miss out on individuals only identified by the NAFLD criteria in the long-term. Hence, we read with great interest that no liver-related deaths occurred in the MAFLD−/NAFLD+ group and that no excess all-cause mortality was observed in fully adjusted models (Figure 1). Similarly, Kim et al., using the same NHANES cohort, also demonstrated that the MAFLD−/NAFLD+ group was not at increased risk of mortality. In fact, in univariable models, this group was at a significantly lower mortality risk (HR, 0.6).[7] This illustrates that the presence of NAFLD alone seems to be a predictor (not a cause) of lower mortality risk, probably driven by the absence of metabolic dysfunction. Because disease management focuses on lifestyle improvements and weight loss, it is unlikely that the NAFLD-only group could benefit from specialists' attention, because this group is by definition metabolically healthy and has no or limited alcohol consumption. This is a strong argument against marking this population as fatty liver disease and argues for spending the resources and attention on populations at higher risk of advanced liver disease and liver-related death.

Using the recently released NHANES data with transient elastography, the authors investigated fibrosis and advanced fibrosis risk factors. Similar to mortality risk, no large differences were observed in risk factors for fibrosis between patients with NAFLD and MAFLD except for overweight/obesity, which was a significant risk factor in NAFLD (HR, 4.5), but not in patients with MAFLD (HR, 2.2). However, we note that the control group might be unstable for this specific analysis, as only 3.6% of patients with MAFLD had no overweight and 4.9% of patients with NAFLD, resulting in wide confidence intervals (e.g., 1.26–15.89). Nonetheless, these findings are interesting, as they indicate that patients with MAFLD without overweight but with metabolic dysfunction are at 50% lower risk of fibrosis, and patients with NAFLD without overweight (and often no metabolic dysfunction) were at 80% lower risk of fibrosis. Given the differences in the control group, the estimates are expected to be different and direct comparison should be done with caution.

As a final discussion point, the authors proposed using fatty liver disease with subcategories such as alcoholic, nonalcoholic, or drug-induced instead of NAFLD or MAFLD. Their newly-presented approach is a fine example of the Dutch "Polder model" that recognizes pluriformity but seeks cooperation despite these differences. As this model enables to govern a diverse country, it might also unite experts and stakeholders on a new definition of fatty liver disease. We want to continue on the authors' proposal to use subcategories within a broader definition. However, we suggest using MAFLD and not fatty liver disease as the umbrella term, because there is emerging evidence indicating that the small MAFLD−/NAFLD+ group is not at risk for advanced liver disease at baseline nor for adverse outcomes in the long-term. As compellingly shown by the authors, ALD is an essential factor in the disease course of fatty liver disease and therefore should be a dedicated subcategory within the MAFLD spectrum. As sole investigators can never reach consensus, an international consensus meeting representing all stakeholders is warranted. At the end, one size still does not fit all and the MAFLD criteria should be further improved by categorizing this population according to their main risk factors or key characteristics.

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CONFLICT OF INTEREST

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