Editorial

NAFLD or MAFLD: the data behind the debate

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Since its introduction in the 1980s (1), there has been substantial growth in the knowledge of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH). This is of utmost importance as the disease burden of NAFLD has grown globally as evidenced by its increase in disability-adjusted life-years when compared to other causes for liver disease regardless of region (2). However, despite great advances, there has been discontent with the nomenclature as it may not perfectly capture this heterogeneous disease entity. In response, an international panel proposed replacing NAFLD/NASH with metabolic (dysfunction) associated fatty liver disease (MAFLD) (3). In MAFLD, diagnosis would focus more on presence of risk factors contributing to metabolic dysfunction in the presence of fatty liver, as opposed to just the exclusion of high alcohol intake. It is noted that although most patients with hepatic steatosis who currently carry the diagnosis of NAFLD likely would also meet the criteria for MAFLD, there is a still a non-negligible number of patients who would only meet the criteria for one or the other (4,5). This proposed change has been met with some controversy and there has been a call for further evidence showing that redefining NAFLD to MAFLD would indeed advance the field as well as a call for a consensus discussion involving not only all the liver societies, but also patient advocacy groups, the pharmaceutical industry, and other stakeholders (6). In a recent study published in the *Journal of Hepatology*, the observations made by Kim *et al.* (7) further adds to the current literature on this topic which can be considered a push towards adopting MAFLD not only as a new term for the same disease, but possibly as a distinct entity compared to NAFLD.

In their article, the authors examine the longitudinal association of NAFLD and MAFLD with all-cause mortality as well as cause-specific mortality in a nationally representative sample of patients in the United States by using the Third National Health and Nutrition Examination Survey (NHANES III). This population-based dataset, which spanned from 1988 to 1994, contains biochemical values, demographic data and liver ultrasonography of US civilians and has been utilized heavily in previous NAFLD studies (5). Of the 13,856 adults, 7,761 patients were included in this study with 6,095 patients excluded due to missing data. Despite this, when compared to the larger NHANES III study, the demographic characteristics in this study remained largely unchanged. It is noted that when assessing cause-specific mortality, the authors were able to only assess cardiovascular disease and cancer, while liver-related mortality information was not available. The authors concluded that while MAFLD is associated with all-cause mortality, the association of NAFLD "per se" with all-cause mortality is unclear and the criteria for MAFLD might lead to selection of a more homogenous patient population, excluding for example, patients with "lean" NAFLD.

Through their findings, the authors observed that there was a strong association between MAFLD and all-cause mortality. This association was maintained with statistical significance after a multivariable analysis adjusting for certain metabolic risk factors. NAFLD patients did show association with all-cause mortality in univariable analysis and when stratified by hyperlipidemia, obesity, or hypertension. However, these patients did not show

statistically significant association with all-cause mortality after multivariable analysis with adjustment for metabolic risk factors. With regards to cause-specific mortality, there was no statistically significant association between NAFLD and both cardiovascular and cancer mortality. Similarly, MAFLD was noted to not be associated with cardiovascular mortality after adjustment for metabolic risk factors. There was no significant association between MAFLD patients and cancer related mortality. However, the specific subgroup of MAFLD+/NAFLD– patients did show significant association with cancer mortality. With regards to advanced fibrosis diagnosed based on various biochemical models, NAFLD and MAFLD patients with estimated advanced fibrosis in general showed an increased risk of mortality compared to those without fibrosis, consistent with available literature.

Despite these promising observations, interpretation of these results should be exercised with caution. Contrary to some of the conclusions stated by the authors, these results can be viewed to show significant similarities between NAFLD and MAFLD, rather than important phenotypic differences. After adjustment of the metabolic risk factors as outlined by the article, NAFLD did not show association with all-cause mortality as evidenced by its steady decrease in hazard ratios. MAFLD exhibited a similar trend of significantly decreasing hazard ratios after adjustment however still maintained statistical significance. Although this may point towards a possible association of MAFLD "per se" and all-cause mortality, one must also query whether a stronger association between MAFLD and metabolic confounders (by definition) leads to remaining residual confounding after adjustments and if further or better adjustments would lead to statistically insignificant results. One such adjustment would be the addition of other confounders that were not mentioned in the article. As an example, the MAFLD+/NAFLD– group was the only group noted to have a statistically significant association with cancer related mortality. However, this patient groups' status of concomitant liver disease (such as level of alcohol consumption and viral hepatitis status) remains unclear in the study. Both alcohol consumption and chronic viral hepatitis are known to increase the probability of cancer and are associated with malignancy (8,9). If adjusted, this could not only weaken the association between this group and cancer specific mortality but also weaken the significance of MAFLD association with all-cause mortality. The available evidence suggests that it is the underlying metabolic risk factors that are associated with mortality in patients with NAFLD or MAFLD and not the hepatic steatosis itself, unless it results in advanced fibrosis (10). Therefore, it is not surprising that the authors found stronger associations between MAFLD and mortality as the MAFLD population, by definition, is more strongly associated with metabolic risk factors. More careful adjustments, such as using propensity score matching, inverse probability of weighting, or doubly robust adjustment methods may help to further delineate if there is a true association between MAFLD "per se" and all-cause mortality in the absence of advanced fibrosis.

Another point of interest lies in the patients that are categorized as MAFLD–/NAFLD+. These patients will show signs of hepatic steatosis however with absent signs of metabolic dysfunction as well as other concomitant liver disease. Due to the absence of metabolic dysfunction, these "lean" NAFLD patients would not be captured with the proposed MAFLD criteria. The pathophysiological cause for "lean" NAFLD remains unclear and may be related with abnormal adipose tissue, changes in gut microbiome, altered body compositions, or genetic factors (11). In their study, the authors noted that this group did not have an increase in all-cause mortality or cardiovascular mortality. However, in recent studies "lean" NAFLD patients were reported to have higher ASCVD score than those with obese NAFLD (12) and "lean" NAFLD has been found to be associated with metabolic syndrome and higher median Framingham risk scores when compared to lean patients without NAFLD (13). The prevalence of these "lean" NAFLD patients is non-negligible and has been described in 10–20% of non-obese Americans. As evidenced by these patients, it may be prudent to also focus on what is beyond just what is commonly thought of with metabolic dysfunction with factors such as obesity, hypertension, or diabetes, and consider the underlying pathophysiologic causes that lead to these various but related manifestations. In doing so, we can properly capture all patients who are at risk and provide the appropriate level of awareness for both patients and clinicians alike.

In conclusion, the nomenclature debate between NAFLD and MAFLD continues. We commend Kim *et al.* in their efforts to further elucidate this topic. In our view, their study confirms the previous findings that the main drivers of poor outcomes in patients with hepatic steatosis

(whether called NAFLD or MAFLD) are the underlying metabolic derangements such as increased central fat mass and insulin resistance, which are in turn caused by an interaction between environmental factors such as diet and lifestyle, and genetic determinants of the disease in different populations (14). The different criteria used to define NAFLD and MAFLD can lead to identification of patient populations with substantial overlap, but small differences in the extremes of the distributions. The relatively small differences in outcomes seen in the study by Kim *et al.* are more likely to be artifacts of incomplete adjustment of confounders and selection bias introduced by using different criteria, rather than a true difference in the underlying disease states. Given the extremely high prevalence of the problem, it might be more effective to focus our attention on increasing awareness among patients and care providers that the presence of "fatty liver", typically found on imaging and regardless of the criteria used to define NAFLD or MAFLD, should lead to a careful assessment of a patient's metabolic health and a long term medical and behavioral plan to decrease risk of future adverse outcomes.

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