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MAFLD vs. NAFLD not an emotional political process - rather Evidence-Based Medicine

We read with interest the letter sent to address our paper [1]. While we respect the author of the letter's views, we would first like to note that we were dismayed and disappointed in the tone of the letter which crossed the boundaries of professional conduct in our opinion. It seems that the debate on the terminology is mirroring the style seen in many areas of social and political conduct where emotion and unfounded attacks on personal integrity rather than data and evidence drive the conversation. It is our hope that we can refrain from slandering each other and focus on the data. With that in mind, we will restrict the remainder of our response to the data and scientific content of the letter submitted.

In our initial article, we compared the difference between non-alcoholic fatty liver disease (NAFLD) and metabolic associated fatty liver disease (MAFLD) in patients with diabetes [1]. While Dr. Méndez-Sánchez *et al.* noted fundamental concerns, they had no criticism of the methodology or the results. Rather their comments were focused on interpretation which we will address below. They claimed that the original manuscript suffered from "interpretive bias," which led to an erosion of the legitimacy of science.

The authors brought up four criticisms, which we will seek to address.

(a) Firstly, Dr. Méndez-Sánchez *et al.* questioned the use of the term "overdiagnosis." We thank them for pointing this out, and we agree that the more appropriate term could be "misdiagnosis." Patients with MAFLD(+)/NAFLD(-) had a higher risk of all outcomes, and this could have been driven by the systemic comorbidities rather than the fatty liver itself. In addition, MAFLD (+)/NAFLD(-) patients with viral hepatitis had a 6.77x increased odds of advanced fibrosis, which was likely to be driven either by the viral hepatitis, or by the combination of viral hepatitis and steatotic liver injury. We believe that when multiple aetiologies are contributing to liver disease, considering them under one diagnostic category is not only scientifically inaccurate but also carries the potential for one of the aetiologies to be overlooked during workup. Furthermore, we do consider patients as "HBV/HCV co-infected" rather than a single virus alone, even though they share the same risk factors of blood borne transmission. Using the term MAFLD may potentially bring up the risk of misdiagnosis, missing alternate additional liver diseases that may be present.

(b) Dr. Méndez-Sánchez *et al.* claimed that the MAFLD definition improved diagnostic / prognostic utility. While we agree that it may have increased the sensitivity of determining all cause outcomes in our study, sensitivity alone does not make prognostication reliable. The use of the term may potentially reduce the specificity of attributing these all-cause outcomes to fatty liver disease. Our study was unable to evaluate the use of the terminology as a biomarker accurately to predict detailed outcomes of the disease, especially liver related outcomes.

(c) Dr. Méndez-Sánchez *et al.* claimed that with using MAFLD, it helped to identify the coexistence of viral hepatitis with fatty liver disease that would have been missed under the "primitive NAFLD definition." We disagree with this point, as the patient would already have been diagnosed with the confounding liver disease. Indeed, genotype 3 of HCV can cause hepatic steatosis, which improves with treatment of the HCV [2]. Using the unifying term of MAFLD may lead to ignorance of other causes of hepatic steatosis, such as alcohol, which require a different strategy to holistically manage the patient. This is akin to diagnosing patients with "viral hepatitis" rather than HBV or HCV, which have differing treatment strategies.

(d) Our team does acknowledge the strengths of the term MAFLD, which does capture the systemic factors and upstream drivers of the disease. The use of a positive diagnostic criteria with MAFLD also does help disease definitions, as pointed out in our initial manuscript. However, the limitations of the use of the term also must be discussed as a part of responsible science.

It is apt that Dr. Méndez-Sánchez *et al.* bring up "interpretive bias." Indeed, the article cited by them elaborates on a previously noted opinion that "at the cutting edge of scientific progress, where new ideas develop, we will never escape subjectivity" [3,4]. We are honored that the authors respect the scientific rigour and presentation of our results. We accept that they may choose to interpret the published results differently. Disagreements are part of scientific discourse, and through healthy disagreement, science can progress [5].

Nevertheless, we do believe that such disagreements should remain collegial, and avoid taking the nature of mudslinging or implying that people with contrarian views practice untrustworthy science.

This is especially so in the debate over the terminology of fatty liver disease, where arguments appear to have become heated on all sides of the debate. We agree with the call for a stronger evidence base, and a clear understanding of the implications of change [6]. Evidence should certainly trump eminence to generate more information to guide the field in choosing a name that best represents the disease. Our research group strives to provide more evidence in this space, and is committed to following the evidence, irrespective of the final nomenclature. We hold fast that any eventual changes in the field should serve to benefit patients and their communities, rather than the personal biases of one or a handful of individuals.

We once again thank the authors for their interest in our manuscript. However, we respectfully maintain that their input does not influence our conclusions.

Declaration of interest

None.

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