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Letters to the editor

Interpretive bias on research evidence: Striving to meet the trustworthiness criteria

To the editor

We read with interest the paper by Muthiah and colleagues [1] on the differential impact of non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction associated fatty liver disease (MAFLD) definitions on long-term outcomes including major adverse cardiovascular events, advanced fibrosis, and all-cause and cardiovascular-related mortality in patients with diabetes. We have fundamental concerns with this work.

It is pivotal to remember that unbiased interpretation of data is as important as performing rigorous experiments and studies. The interpretation of data can itself result in bias, so-called "interpretive bias", which can affect reporting and leads to questionable conclusions [2]. Interpretive bias can be driven by two well-known types of bias, namely the "wish" bias of individuals and confirmation bias [2].

"Wish" bias is the tendency for people to interpret information according to their wishes or beliefs and has been demonstrated in the past for several societal and scientific efforts, irrespective of topic [3,4]. A long recognized phenomenon in human psychology, such bias distorts the results of a study and reduces its reliability[3,4]. Confirmation bias on the other hand is the tendency of people to interpret information in a way that conforms to their expectations. Confirmation bias can be large and can also influence the interpretation of results [5]. Clinical research is particularly susceptible to such systematic biases and lapses in conduct due to the infiltration of financial and intellectual conflicts of interest, among other factors [2].

In this work [1], the authors observed that the MAFLD definition increased fatty liver diagnosis by 68.89%. Patients who were classified as MAFLD (+)/NAFLD(-) were at a higher risk of major adverse cardiovascular events, advanced fibrosis, and all-cause and cardiovascular-related mortality compared to MAFLD(+)/NAFLD(+). Viral hepatitis had a synergistic impact with MAFLD in increasing the risk of advanced fibrosis and all-cause mortality. However, in spite of these results, the authors concluded from their data that (a) it was premature to change to MAFLD as it results in an over-diagnosis of fatty liver, (b) MAFLD exaggerated mortality and morbidity in patients with T2DM, (c) the definition of MAFLD causes further heterogeneity in fatty liver disease by including patients with other liver diseases, and (d) while NAFLD focuses on the liver, a limitation in MAFLD is that it seeks to capture systemic factors associated with hepatic steatosis. They conclude that the increased risk of adverse events might not be an accurate representation of a derivative risk from fatty liver but a result of systemic comorbidities associated with the condition. Going through their claims systematically.

According to the textbook definition "Overdiagnosis" is the diagnosis of disease that will never cause symptoms or death during a patient's ordinarily expected lifetime and thus presents no practical threat regardless of being pathologic" [6]. How can this fit with the authors sentence that patients with MAFLD (+)/NAFLD(-) are at a higher risk of all outcomes compared to MAFLD(+)/NAFLD(+), consistent with other studies [7]. Obviously, it is not overdiagnosis, but rather that MAFLD improves diagnosis by capturing the previously missed cases when using the NAFLD definition

According to the definition "exaggerated" means represented as larger, better, or worse than in reality. Does the MAFLD definition exaggerate the outcome or capture it better? If you have two biomarkers or scores and one of them has a high diagnostic or prognostic utility, does this mean this biomarker exaggerated the outcome or that it improved the diagnostic/prognostic utility? The authors' data suggests that the MAFLD definition improves diagnostic/prognostic utility.

According to the authors', viral hepatitis has synergistic effects with MAFLD on the outcomes. They state, "This is unsurprising given the presence of dual liver aetiology resulting in higher mortality". Is it not a good thing that the MAFLD definition helped identify its coexistence with other liver diseases that were previously missed under the primitive NAFLD definition? Again, is not coexistence of liver diseases a real life entity that we see in clinics on a daily basis?

Ultimately, they claim that MAFLD seeks to capture systemic factors associated with hepatic steatosis, while NAFLD focus on liver. The centre-point of MAFLD is that it identifies pathophysiology and we treat the patient not the organ. If the revolutionary change from NAFLD to MAFLD has not done anything, attracting attention to the systemic nature of the condition is a win for patients and for Hepatology.

Going through other similar articles from the same group of authors tells us that theirs is a systematic pattern, not a random error of interpretation. One wonders whether this bias in the interpretation offers opportunities to study what happens to the process of consensus on fatty liver disease redefinition when self-speaking results are deliberately misinterpreted. This questions the objectivity of the entire discipline of consensus processes [8,9]. Moreover, it can be difficult to discern whether consensus is based on careful consideration of all the evidence and its accurate interpretation, inappropriate entrenchment of old information, lack of dissemination of newer data, or purposeful silencing of their existence.

In conclusion, efforts should be redoubled to increase awareness within the scientific and academic community to improve adherence to transparent reporting and interpretation as a crucial aspect of data integrity, exactly as when performing the study. Accuracy in interpretation should be taken seriously as otherwise it leads to an erosion in the perceived legitimacy of science as an impartial means of finding the truth.

Declaration of interest

None.

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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].