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PII: S0168-8278(21)02032-8
Reference: JHEPAT 8426

To appear in: Journal of Hepatology

Received Date: 2 September 2021
Accepted Date: 3 September 2021

Please cite this article as: De A, Ahmad N, Mehta M, Singh P, Duseja A, NAFLD Vs MAFLD – It is not the name but the disease that decides the outcome in fatty liver, Journal of Hepatology (2021), doi: https://doi.org/10.1016/j.jhep.2021.09.002.

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Electronic word count: 799

Number of figures: 1

Conflict of interest: none

Financial support: none

Authors contributions: Ar De: manuscript writing, data analysis and critical revision, NA-writing, MM: data curation and analysis, PS: data curation and analysis, AD: data curation and critical revision
Sir,

We read with great interest the study by Kim et al who analysed the NHANES III (National Health and Nutrition Examination Survey) cohort and provided interesting insights into the prognostic outcomes of metabolic dysfunction-associated fatty liver disease (MAFLD) and non-alcoholic fatty liver disease (NAFLD) (1).

It is intriguing to note that out of 13,856 patients in the NHANES III cohort with ultrasound assessment of hepatic steatosis, 1193 (8.6%) patients were excluded because of missing laboratory variables like triglycerides, HDL and high sensitivity-C-reactive protein (hs-CRP) (1). An additional 4875 (35.2%) patients were further excluded as they did not fast for 8 hours or did not have fasting levels of glucose or insulin (1). As per MAFLD criteria, the definition of metabolic-dysfunction in non-diabetic patients with normal BMI requires a battery of investigations, some of which like hs-CRP and HOMA-IR are not routinely ordered in patients being evaluated for hepatic steatosis in clinical practice (2). To address this issue, we retrospectively reviewed data of 1040 patients with NAFLD [mean age 40.9± 11.3 years, 604 (58%) males] managed prospectively in a real-life fashion over the last 10 years at our institute for the presence of MAFLD. Asian cut-offs for BMI and waist circumference was used for defining overweight and central obesity. Nine-hundred and sixteen (88%) patients had BMI≥23 kg/m² and/or type 2 diabetes mellitus (T2 DM) and qualified as MAFLD. Of the remaining 124 (12%) non-diabetic lean patients, hs-CRP was not available in any patient while HOMA-IR was available in only 7 (5.6%) patients. Despite the unavailability of these parameters, ≥ 2 of 7 criteria for metabolic-dysfunction were present in 48 of these 124 (38.7%) patients who were labelled as lean MAFLD. However, in the absence of HOMA-IR and hs-CRP levels, it was not possible to determine if the remaining 76 (61.3%) lean, non-diabetic...
patients with underlying NAFLD had MAFLD (Figure 1). Our observations suggest the poor applicability of MAFLD criteria in real-life clinical practice. Indeed, a substantial number of such non-diabetic, lean patients with hepatic steatosis may not be evaluable using current MAFLD criteria in the real world due to the lack of all laboratory parameters.

The authors reported that MAFLD was associated with increased all-cause mortality after adjusting for metabolic risk factors, while NAFLD was not (1). Further, the adjusted increase in mortality appeared to be predominantly due to an increase in cancer mortality rather than cardiovascular mortality. Unfortunately, the data on liver related mortality was not available.

It is important to note that all patients with MAFLD (+)/NAFLD (-) had a second etiology for liver disease (1). The proportion of patients with significant alcohol consumption or chronic viral hepatitis has not been mentioned. Both alcohol and chronic viral hepatitis are pro-oncogenic and have been associated with a number of malignancies (3, 4). While the authors have adjusted their calculations for traditional risk factors and metabolic co-morbidities, they have not adjusted for significant alcohol consumption or viral hepatitis. This makes us wonder if the presence of other concomitant etiology may have contributed to the excess all-cause and cancer-related mortality in MAFLD. The presence of a second etiology may also explain why the weighted prevalence of advanced fibrosis (9.22%) in the group of patients with MAFLD (+)/NAFLD (-) was substantially higher than those with MAFLD (+)/NAFLD (+) (2.61%) and MAFLD (-)/NAFLD (+) (0.47%), respectively. Hence, data on liver related mortality is required for further granular understanding of the differences between MAFLD and NAFLD.

The etymological debate on MAFLD vs NAFLD revolves around the etiology of liver disease and should be driven primarily by pathophysiological concerns rather than prognostic endpoints (5). Different subtypes or stages of a particular disease may have varying prognosis but
should be categorised under a single etiology. Putative pathophysiological drivers in lean patients with MAFLD (-)/NAFLD (+) like gut microbiota and genetics also play a role in MAFLD (+)/NAFLD (+) (6, 7). It should also be noted that patients with lean NAFLD patients are usually younger than those with the classical NAFLD phenotype who also qualify as MAFLD (8, 9). In the present study too, patients with MAFLD (-)/NAFLD (+) were almost a decade younger (35.0 ± 0.9 years) than those with MAFLD (+)/NAFLD (+) (47.2 ± 0.6 years) (1). It is plausible that the subtle metabolic derangements in these young patients with MAFLD (-)/NAFLD (+) is not yet severe enough to be clinically discernible but will become so with passage of time. Indeed, in a community-based study, patients with MAFLD (-)/NAFLD (+) had a significantly higher risk of developing new onset diabetes mellitus compared to controls with an adjusted relative risk of 2.2 (10).

In conclusion, the debate on the nomenclature of NAFLD vs MAFLD is far from over. It is not the name but the disease that decides the outcome of patients with fatty liver disease.

References


Legend to figure:

Figure 1: Poor applicability of MAFLD criteria in lean, non-diabetic patients with NAFLD

(T2 DM: type 2 diabetes mellitus; BMI: body mass index; NAFLD: non-alcoholic fatty liver disease; MAFLD: metabolic dysfunction-associated fatty liver disease)
Total number of patients with NAFLD: 1040

- Overweight/obese with or without T2 DM [n=891; overweight= 194 (21.7%), obese= 697 (78.2%), concomitant T2 DM= 152 (17.1%)]
- T2 DM with normal BMI (n=25)
- Lean NAFLD without T2 DM (n=124)
  - Lean, non-diabetic with metabolic dysfunction (n=48)
  - Inadequate data for categorisation using MAFLD criteria (n=76)