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Deciphering the implications of MAFLD and MASLD definitions in the NAFLD population: results from a single-center biopsy study

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To the Editor: The nomenclature for steatotic liver disease has been a topic of debate since 2020. The conventional expression, non-alcoholic fatty liver disease (NAFLD), was introduced in 1980 to describe the occurrence of steatosis in the absence of other hepatic diseases. However, in recent years, there has been a growing movement to phase out and retire this term. In 2020, Eslam *et al*[1] proposed a new definition — metabolic (dysfunction) associated fatty liver disease (MAFLD) — redefining the disease to include hepatic steatosis along with other factors such as diabetes, obesity, overweight, or meeting the criteria for metabolic dysfunction. The transition from NAFLD to MAFLD was deemed necessary for several reasons, including the inability of NAFLD to clearly explain the disease's pathophysiology, the possibility of patient stigma due to the term "alcoholic," potential miscommunication between patient and physician, and a preference for defining the disease by positive diagnostic criteria rather than through exclusion.[1] Although MAFLD and NAFLD did not correspond to the identical population, there was a high consistency between NAFLD and MAFLD.[2] The shift in terminology without comprehensive understanding of its implications has also been met with resistance, mainly due to the potential confusion it could cause. In an effort to conclude the ongoing debate, a team of 236 experts from 56 different countries endeavored to pinpoint a new, more appropriate name to supersede the term NAFLD. The consensus reached was to rename the condition as metabolic dysfunction-associated steatotic liver disease (MASLD). The definition of MASLD includes the presence of steatosis paired with a minimum of one of five predetermined cardiometabolic criteria. The existence of cardiometabolic factors in conjunction with secondary etiologies has been categorized separately from MASLD.[3]

The present analysis aimed to investigate the applicability and agreement of the MAFLD and MASLD definitions in a population with biopsy-proven NAFLD at a single tertiary care center. The overarching goal was to enhance understanding of the implications of the revised nomenclature on patients with NAFLD and provide valuable insights into its potential impact on this clinical population.

We carried out a retrospective analysis of data prospectively gathered from 678 patients, each with biopsy-confirmed NAFLD. These patients were diagnosed and monitored at a tertiary care institution, the Gastroenterology Outpatient Facilities of the Marmara University, between 2009 and 2010, and from 2017 to 2023. The study variables, comprising demographic and laboratory data along with liver biopsy examinations, were sourced from the Turkish NAFLD Biobank electronic database maintained by the Marmara University Institute of Gastroenterology. Patients with viral hepatitis, drug-induced liver disease, autoimmune hepatitis, or metabolic/genetic liver diseases, or those consuming significant amounts of alcohol (>20 g daily for women and >30 g for men), were excluded from this data set. The patients were classified as NAFLD, MAFLD, and MASLD following the recommended diagnostic criteria.[1,3,4] The diagnostic approach is demonstrated in Supplementary Figure 1, http://links.lww.com/CM9/B941. We utilized the Cohen's kappa statistic as a tool to gauge the level of agreement between the MAFLD and MASLD nomenclatures. In general, kappa values between 0.41 and 0.60 are considered moderate, those between 0.61 and 0.80 are considered satisfactory, and those that are greater than 0.81 are considered perfect. Analyses were performed using Statistical Package for the Social Sciences, version

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24.0 (IBM, Armonk, NY, USA), with all tests two-sided at a 5% level of significance.

The characteristics of the study population and liver biopsy results are presented in Supplementary Table 1, http://links.lww.com/CM9/B941. When applying the high National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) waist circumference thresholds of ≥102/88 cm for Caucasian men and women, 670 patients with NAFLD (98.8%) were determined to have MAFLD. Similarly, when utilizing the low American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) waist circumference thresholds of ≥94/80 cm, 671 patients with NAFLD (99.0%) were classified as having MAFLD. Out of the entire NAFLD cohort (n = 678), 640 (94.4%) patients were diagnosed with MAFLD due to their body mass index (BMI) exceeding the 25 kg/m^2 threshold and 301 (44.4%) were found to have type 2 diabetes. There were 25 patients with NAFLD who did not meet any of these criteria. However, 17 of them were still classified as having MAFLD because they exceeded the metabolic dysfunction criteria with waist circumferences ≥102/88 cm. In addition, 18 patients had waist measurements ≥94/80 cm. Among the eight patients with NAFLD who did not meet the MAFLD criteria — because they were lean with fewer than two metabolic risk factors — six were classified as F0, one as F1, and one as F3.

We identified 676 patients (99.7%) with NAFLD who fulfilled the diagnostic criteria for MASLD. Of these patients, 514 (75.9%) were found to have type 2 diabetes or a fasting blood glucose level equal to or above 100 mg/dL or HbA1c greater than or equal to 5.7%. Additionally, 541 (80.3%) had elevated high density lipoprotein (HDL) levels or were on lipid-lowering treatment, while 655 (96.6%) had a BMI greater than or equal to 25 kg/m^2 or had an increased sex-specific waist circumference of more than 94/80 cm, with 651 (96%) for greater than or equal to 95/91 cm. Moreover, 421 (62.1%) patients exhibited increased blood pressure levels or were undergoing antihypertensive treatment, and 513 (75.7%) had elevated triglyceride levels or were on lipid-lowering therapy. Interestingly, the patients' waist circumference did not seem to affect the MASLD diagnosis. Two patients (0.3%) were diagnosed with NAFLD but not MASLD. This was due to the lack of any discernible cardiometabolic criteria. One of these patients had fibrosis stage F1, while the other was diagnosed with metabolic dysfunction-associated steatohepatitis (MASH). None of these two patients met the criteria for MAFLD. After eliminating secondary causes, the two patients were diagnosed with cryptogenic steatotic liver disease.

The Cohen's kappa values, utilized to gauge the degree of agreement between the MAFLD and MASLD definitions, obtained using the NCEP-ATP III and AHA/NHLBI thresholds for waist circumference (≥102/88 cm and ≥94/80 cm, respectively), were 0.397 and 0.442, respectively. These values indicate an overall moderate level of agreement.

In our single-center investigation, we assessed the applicability of two newly proposed nomenclatures, MAFLD and MASLD, designed to replace the current NAFLD terminology, within a clinical cohort with biopsy-confirmed NAFLD. Our findings suggest that both the MAFLD and MASLD terminologies align well with the presence of biopsy-proven NAFLD, with a compatibility rate of up to 99% for both classifications. Interestingly, our study revealed that nearly all patients with NAFLD were reclassified as MASLD, with the exception of two patients being identified as cryptogenic cirrhosis.

While ongoing efforts to redefine hepatic steatosis are commendable, the sudden shifts in its definitions could potentially lead to confusion. Currently, the main disadvantage of the MAFLD and MASLD definitions is the inadequate understanding of whether they are applicable in the traditional NAFLD population. A recent research by Song *et al*[5] demonstrated negligible differences between the various definitions, and these findings are echoed in our study. Specifically, in their population screening study of 1016 apparently healthy individuals, the prevalence rates for NAFLD, MASLD, and MAFLD were 25.7%, 26.7%, and 25.9%, respectively. In addition, out of their 414 histologically confirmed patients with NAFLD, only one patient failed to meet the MASLD criteria and six did not meet the MAFLD criteria,[5] a finding that aligns with our results.

To our knowledge, this study represents a pioneering comprehensive examination of the MAFLD and MASLD criteria reported from Turkey in a sizable cohort of patients with biopsy-proven NAFLD. Our findings suggest that the data collected on NAFLD can be optimally utilized within the new MASLD framework. The substantial overlap observed between NAFLD and MASLD is not coincidental; rather, it is a deliberate part of recent efforts to update the nomenclature. As the majority of patients diagnosed with NAFLD fall under the MASLD label, the ongoing clinical drug trials and biomarker studies remain unaffected by this name change. However, it is crucial to exercise caution when interpreting our findings. All patients included in our study were of Turkish descent, necessitating validation in diverse populations. In addition, it is important to consider that our data might not be applicable to the general population, as our study specifically included patients at a higher risk of developing severe liver disease who underwent liver biopsy.

In conclusion, we found that the MAFLD and MASLD criteria identify a similar population to NAFLD, but MASLD appears to accommodate a larger number of patients with biopsy-proven NAFLD. Policymakers should advocate for initiatives aimed at defining steatotic liver disease in accordance with clinical necessities. Additional longitudinal studies are required to shed further light on the implications of the terminology changes.

Ethics approval

The study protocol adhered to the ethical guidelines set forth in the *Declaration of Helsinki* and received approval

from the Medical Ethics Committee of Marmara University School of Medicine (protocol No. 09.2018.086). Patient consent was waived due to the retrospective nature of the study.

Conflicts of interest

None.

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