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Letters to the editor

Impact of new fatty liver disease nomenclature on primary care— cerebration of gastroenterologists in a regional tertiary care hospital

Dear Editor,

We read the study by Rinella *et al.* [1] with great interest, which is a significant advance in the liver disease research field. The authors proposed to use steatotic liver disease (SLD) recapitulating hepatic steatosis of various etiologies, metabolic dysfunction-associated steatotic liver disease (MASLD) replacing nonalcoholic fatty liver disease (NAFLD), and MetALD distinguishing MASLD patients who intake more alcohol (140 to 350 g/week and 210 to 420 g/week for females and males respectively). It will help hepatologists, clinicians, and patients better understand, manage, and treat diseases. Here, we pondered the impact of new fatty liver disease nomenclature on primary care /community health care.

First, long-term surveillance management of any chronic disease will fall to community health care. With the promotion of ultrasound in primary care, community clinicians can better identify MASLD and establish health records for residents. Adding "metabolic dysfunction" to disease nomenclature can make clinicians calmer when explaining the condition to patients and convince patients when doing health education to patients. For example, for nonalcoholic steatohepatitis (NASH) patients with a high risk of advanced fibrosis, guidelines recommend using pioglitazone, a thiazolidinedione, or vitamin E to improve liver pathology and cardiovascular metabolism[2,3]. Previously, clinicians had to explain to patients the rules and reasons for using such drugs, and this process was much easier after renaming. Before renaming, clinicians faced with NAFLD patients with alcohol consumption needed to make seemingly contradictory diagnoses of "NAFLD" and "alcohol-related liver disease (ALD)." At the same time, the newly added MetALD avoided this embarrassment.

Second, replacing the exclusive, stigmatized terms "nonalcoholic" and "fatty" with the positive, descriptive "metabolic dysfunction" and "steatosis" makes it more acceptable for patients, especially adolescent pediatric patients. More importantly, it is easier for patients to understand and accept health education about MASLD and work with clinicians to manage it.

However, it is arduous for a new name for a disease to be accepted by the public overnight, which requires community clinicians to study at top medical institutions in the region from time to time and pay real-time attention to the latest advances in medical knowledge. Due to habits, ongoing clinical trials, published document literature, and others, it may still take 5-10 years for MASLD to replace NAFLD completely.

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Declaration of interests

None.

Author contributions

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Prevalence and mortality prognosis of steatotic liver disease phenotypes

To the editor,

We read the new nomenclature for steatotic liver disease (SLD) with great interest [1]. Given the existence of phenotypic heterogeneity of fatty liver, the extent to which these innovative SLD phenotypes (i.e., metabolic dysfunction-associated steatotic liver disease [MASLD], alcohol-related liver disease [ALD], and an overlap of the 2 [MetALD]) were associated with adverse events remains unclear.

We utilized data from the Third National Health and Nutrition Examination Survey (NHANES III), which comprised data on ultrasonography-measured steatosis [2]. The ethical review board of the National Center for Health Statistics approved the implementation of

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NHANES. Each participant provided information on alcohol consumption through a questionnaire [2]. In NHAENS, a drink means a 12-oz beer, a 4-oz glass of wine, or an ounce of liquor, which could be converted to 14 grams of pure alcohol [3]. In this study, as suggested by the consensus [1], MetALD patients were classified into a category distinct from MASLD to capture the pathogenic value of alcohol consumption and prognostic implications [1]. Participants were followed for the all-cause mortality by the National Death Index records were reviewed on December 31, 2019.

Our analysis included 6279 participants from NHANES III who were then categorized into five groups: (1) MASLD, *N*=872, (2) MetALD, *N*=141, (3) ALD, *N*=64, (4) Other SLD, *N*=108, and (5) Participants without hepatic steatosis, *N*=5094. We used a multivariable-adjusted Cox proportional hazard regression model to assess the association of these SLD phenotypes with all-cause mortality, with models accounting for demographic and cardiometabolic risk factors. P values were 2-sided and considered significant at 0.05. All analyses were performed by using R, version 4.2.1.

As shown in Table 1, in this large and nationally representative US cohort consisting of 6279 adults (age 48.1±20, 53 % female), the prevalence of MASLD was 13.8 %, MetALD was 2.2 % and ALD was 1.0. After a median follow-up of 26.9 years, 1892 all-cause deaths were documented. We observed that ALD was significantly associated with a 69 % higher hazard of all-cause mortality (hazard ratio [95 % confidence interval], 1.69 [1.18 −2.41], *P*<0.001) when compared with healthy controls, while the association between other SLD phenotypes and mortality are neutral (*P for all* >0.1).

Previous studies have demonstrated the association between metabolic dysfunction associated with fatty liver disease and all-cause mortality [2]. However, as metabolic dysfunction related to fatty liver disease does not entirely exclude ALD [4], the role of alcohol intake in SLD patients remains unclear. Our study expanded prior findings and, for the first time, showed that, for SLD patients, alcohol intake may play a more critical role than metabolic dysfunction in association with all-cause mortality. Considering that alcohol consumption was one of the leading causes of death and disability worldwide [5]. Our study further highlights the impact of alcohol consumption on mortality in SLD patients. Restricting alcohol consumption may be a crucial measure in reducing the mortality of SLD patients. The new nomenclature may provide important insights into risk stratification from an alcohol-related pathophysiological pathway. It should be noted that the population studied in the NHANES III database was examined between 1988 and 1994; the dynamic evolution of SLD during follow up was not captured in this study. More studies are warranted to validate our findings.

Author contributions

HJ, ZS, JG-Conceptualization, HJ, ZS - Data curation, HJ, ZS- Formal analysis, HJ- Funding acquisition, All authors- Investigation, All authors - Methodology, JG - Project administration, JG, HJ- Resources, HJ, ZS-Software, HJ- Supervision, HJ- Validation, HJ- Visualization, All authors-Writing - original draft, All authors - Writing - review & editing.

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Declaration of interests

None.

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Table 1
Prevalence and mortality prognosis of steatotic liver disease phenotypes.

	Overall	No Steatosis	MASLD*	MetALD*	ALD	Other SLD	P
N	6279	5094	872	141	64	108	
Events, n (%)	1892 (30.1)	1472 (28.9)	310 (35.6)	67 (47.5)	32 (50.0)	11 (10.2)	<0.001
Adjusted Hazard Ratio# (95% CI)	-	Reference	0.94 (0.82, 1.06)	1.19 (0.93, 1.52)	1.69 (1.18, 2.41)	0.86 (0.47, 1.56)	0.029

MASLD, metabolic dysfunction-associated steatotic liver disease; ALD, alcohol-related liver disease; CI, confidence interval.

* The five cardiometabolic criteria evaluated as specified by Rinella *et al.* (1) Systolic blood pressure ≥ 130 mmHg or diastolic ≥ 85 mmHg, or use of antihypertensive medication. (2) Blood glucose ≥ 100 mg/dL or HbA1c ≥ 6.5%, or presence of type 2 diabetes or diabetes treatment. (3) BMI ≥ 25 or waist circumference > 94 cm (males), > 80 cm (females). (4) HDL cholesterol ≤ 40 mg/dL (males), ≤ 50 mg/dL (females), or lipid-lowering treatment. (5) Triglycerides ≥ 150 mg/dL or intake of lipid therapy.

Other SLD represents those who had non-alcoholic SLD without metabolic dysfunction.

Models adjusted for age, sex, current smoking, systolic blood pressure, antihypertensives, diabetes mellitus, diabetic medication, body mass index, total cholesterol, high-density lipoprotein cholesterol, lipid lowering therapy, race and family income.

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MASLD identifies patients with significant hepatic fibrosis and steatosis in fatty liver population

To the editor,

We have read with interest the article by Rinella ME *et al.* [1], in which metabolic dysfunction-associated steatotic liver disease (MASLD) has been proposed as a novel diagnostic term that differs from non-alcoholic fatty liver disease (NAFLD). The original name change from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) has successfully reduced the stigma associated with the condition and emphasized its close connection with metabolic disorders [2–4]. However, the definition of MAFLD is complex, and some subitems, such as HOMA-IR and high-sensitivity C-reactive protein (hs-CRP), are not routinely measured in clinical practice across regions, which leads to underdiagnosis and delayed treatment [5,6]. The proposed name change to MASLD, which optimizes the MAFLD definition, is simplified and acceptable. MASLD is defined by inclusion rather than exclusion criteria and is diagnosed in patients with hepatic steatosis and metabolic risk factors. However, its practicality and effectiveness have not been tested and validated in real-world settings. We aimed to identify MASLD patients and compare the characteristics of MASLD and non-MASLD steatosis patients.

Our study involved 9406 patients diagnosed with fatty liver by ultrasound for analysis. Of them, 9240 (98.2%) patients were diagnosed with MAFLD and MASLD overlapping, and 95 (1.0%) patients were classified as MASLD but undiagnosed MAFLD due to the lack of hs-CRP and insulin. And 71 (0.8%) patients were identified as non-MASLD but undiagnosed MAFLD patients (Fig. 1A). In addition, MASLD patients were older, predominantly male, and exhibited a higher prevalence of metabolic disorders and elevated liver enzymes compared with non-MASLD patients. Additionally, the MASLD group displayed significant liver steatosis and fibrosis (Table S1), including elevated HSI [37.31 (34.77, 40.22) vs. 35.00 (32.35, 37.82), $p<0.001$], FLI [1.80 (0.81, 4.17) vs. 0.14 (0.09, 0.24), $p<0.001$], FIB-4 [0.97 (0.69, 1.34) vs. 0.51 (0.37, 0.78), $p<0.001$] and NFS [−2.06 (−2.96, −1.11) vs. −3.85 (−4.58, −3.26), $p<0.001$] (Fig. 1B). These findings highlight the importance of accurately identifying and treating MASLD patients to prevent further liver damage and improve outcomes.

[1] Last authors.