A simpler definition of MAFLD better predicts long-term all-cause mortality in American adults

Jiarong Xie, Linjie Lu, Yishu Chen, Lei Xu, Chengfu Xu

PII: S0168-8278(22)00028-9
DOI: https://doi.org/10.1016/j.jhep.2022.01.015
Reference: JHEPAT 8586

To appear in: Journal of Hepatology

Received Date: 9 January 2022
Accepted Date: 14 January 2022

Please cite this article as: Xie J, Lu L, Chen Y, Xu L, Xu C, A simpler definition of MAFLD better predicts long-term all-cause mortality in American adults, Journal of Hepatology (2022), doi: https://doi.org/10.1016/j.jhep.2022.01.015.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.
A simpler definition of MAFLD better predicts long-term all-cause mortality in American adults

Authors: Jiarong Xie\textsuperscript{1,2,3,†}, Linjie Lu\textsuperscript{1,2,4,†}, Yishu Chen\textsuperscript{1,2}, Lei Xu\textsuperscript{1,2,3}, Chengfu Xu\textsuperscript{1,2,4,*}

Authors’ affiliations:
\textsuperscript{1}Department of Gastroenterology, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China.
\textsuperscript{2}Zhejiang Provincial Clinical Research Center for Digestive Diseases, Hangzhou, China
\textsuperscript{3}Department of Gastroenterology, Ningbo First Hospital, Ningbo, China.
\textsuperscript{4}Department of Gastroenterology, Haining Branch of the First Affiliated Hospital, Zhejiang University School of Medicine, Haining, China.

*Corresponding author:
Dr. Chengfu Xu, Department of Gastroenterology, the First Affiliated Hospital, Zhejiang University School of Medicine. No. 79 Qingchun Road, Hangzhou 310003, China. Phone: 0086-571-87236863; E-mail: xiaofu@zju.edu.cn

† Jiarong Xie and Linjie Lu contributed equally to this work.

This Letter to the Editor is in response to:
The title of the original paper: Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States

The corresponding author of the original paper: Donghee Kim, Peter Konyn

E-mail addresses: messmd@chol.com, dhkimmd@stanford.edu (D. Kim)

Conflict of interest statement: None.

Authors' contributions: Study concept and design: C. Xu. Acquisition of data: J. Xie, L. Lu, and Y. Chen. Analysis and interpretation of data: J. Xie, L. Lu, Y. Chen, L. Xu, and C. Xu. Drafting of the manuscript: J. Xie, L. Lu, Y. Chen, and C. Xu. Critical revision of the manuscript for important intellectual content: C. Xu. Obtained funding: J. Xie, and C. Xu. Study supervision: C. Xu.

Financial support: This work was supported by the National Natural Science Foundation of China (82070585, 81770573, 81722009), Key Research and Development Program of Zhejiang Province (2020C03033), National Key Research and Development Program (2018YFA0109800), “Ten thousand plan”-High Level Talents Special Support Plan of Zhejiang Province (ZJWR0108008), Zhejiang Provincial Program for the Cultivation of High-Level Innovation for Health Talents, Natural Science Foundation of Ningbo (202003N4233), and Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (2021KY991).
To the editor:

We read with great interest the article by Kim et al [1], showing that metabolic dysfunction-associated fatty liver disease (MAFLD) was associated with an increased risk of all-cause mortality in a large nationally representative population of the United States. They also found that advanced fibrosis in MAFLD was associated with higher estimates for all-cause mortality than in NAFLD.

MAFLD is a novel definition proposed in 2020 [2], the diagnosis of which requires the presence of fatty liver in addition to any of overweight/obesity, type 2 diabetes mellitus, or evidence of metabolic dysregulation. Although MAFLD was associated with an increased risk of all-cause mortality, some lean MAFLD patients may not be at high risk of metabolism-related death. Besides, the MAFLD definition is complex and some subitems, such as HOMA-IR and hs-CRP, are not routinely measured in primary healthcare centers. Therefore, it is imperative that the MAFLD definition be validated and optimized in real-world practice, and a more simplified and applicable set of criteria is highly needed.

Here, we developed a simplified set of metabolic syndrome (MetS)-based criteria for MAFLD, and compared the performance of the simplified criteria with that of the original criteria in predicting all-cause mortality in a 27-year follow-up of American adults. The dataset used in our analysis was the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994, which recruited a representative sample of the US population using a complex, multistage probability design [3]. The follow-up data and mortality status were updated to 31 December, 2015.
Considering that metabolically healthy obese individuals have a low risk of developing metabolic diseases [4], and waist circumference is widely regarded as an independent risk factor for MetS and also the only component of MetS that is associated with the presence of NAFLD and liver fibrosis [5, 6], we combined BMI and waist circumference as one indicator of obesity/central obesity in the simplified criteria. As both T2DM and prediabetes refer to abnormal blood glucose, we combined T2DM and prediabetes indicators into one criterion rather than list it as a separate category. Similarly, given that the majority of individuals with HOMA-IR scores ≥2.5 had at least two metabolic abnormalities (Figure 1A), we did not list HOMA-IR score separately either. Besides, because hs-CRP, an indicator of relatively low specificity, is not routinely measured in clinical practice across regions, we propose that it be excluded from the diagnostic criteria, echoing an expert consensus from the Middle East and North Africa [7]. Moreover, as emerging evidence has suggested the critical role of hyperuricemia in the development of fatty liver [8-10], we included hyperuricemia in the simplified criteria.

To sum up, our simplified MetS-based criteria of MAFLD are described as the presence of fatty liver combined with at least two of the following conditions: (i) obesity/central obesity: BMI ≥25 kg/m², or waist circumference ≥102/88 cm in US males and females, respectively; (ii) elevated blood pressure: blood pressure ≥130/85 mmHg or specific drug treatment; (iii) elevated TG: TG ≥150 mg/dL or specific drug treatment; (iv) hyperglycemia: prediabetes or diabetes, or specific drug treatment; (v) hyperuricemia: serum uric acid >7 mg/dL in males or >6 mg/dL in females, or specific
drug treatment; and (vi) HDL-cholesterol <40 mg/dL for males and <50 mg/L for females or specific drug treatment. By utilizing UpSet plot, we visualized the intersections and their aggregates, the number of potential predictors, and the attribute statistics (Figure 1A). Of the 4,414 participants diagnosed with fatty liver who were included for analysis, 3,756 met the MAFLD-original criteria, and 3,384 met the simplified MAFLD criteria (Figure 1B). Kaplan-Meier analysis confirmed that fatty liver individuals who met the simplified criteria had a significantly higher risk of all-cause mortality than those who met the original criteria (MAFLD-simplified vs. MAFLD-original: $P = 0.02$) (Figure 1C). Compared with fatty liver individuals who did meet the MAFLD-original criteria (MAFLD-original-free), the HR (95% CI) was 1.252 (0.943–1.663) for all-cause mortality in MAFLD-original individuals after adjustment for age, sex, and race/ethnicity ($P = 0.117$). Meanwhile, the corresponding HR (95% CI) was 1.628 (1.222–2.170) in MAFLD-simplified individuals, compared with MAFLD-simplified-free individuals ($P = 0.001$) (Figure 1C). These findings showed that the simplified criteria were superior in predicting all-cause mortality in American adults with fatty liver disease.

In conclusion, the MAFLD-simplified definition proposed in our study could serve as an optimized risk stratification tool for predicting all-cause mortality in fatty liver individuals. The simplified diagnostic process may better identify high-risk MAFLD individuals in clinical practice.
References


Figure Legends

Figure 1. (A) Upset plot for each diagnostic indicator; (B) Venn diagram in the population with fatty liver. MAFLD, metabolic dysfunction-associated fatty liver disease; (C) Kaplan Meier analysis for all-cause mortality of MAFLD participants met different criteria.
Participants with fatty liver

\[ (n = 4,414) \]

- MAFLD-original only
  - 8.6% \( (n = 379) \)
- MAFLD-simplified only
  - 0.2% \( (n = 7) \)
- MAFLD-overlapping
  - 76.5% \( (n = 3,377) \)

All-cause mortality

MAFLD-simplified vs. MAFLD-original: \( P = 0.02 \)