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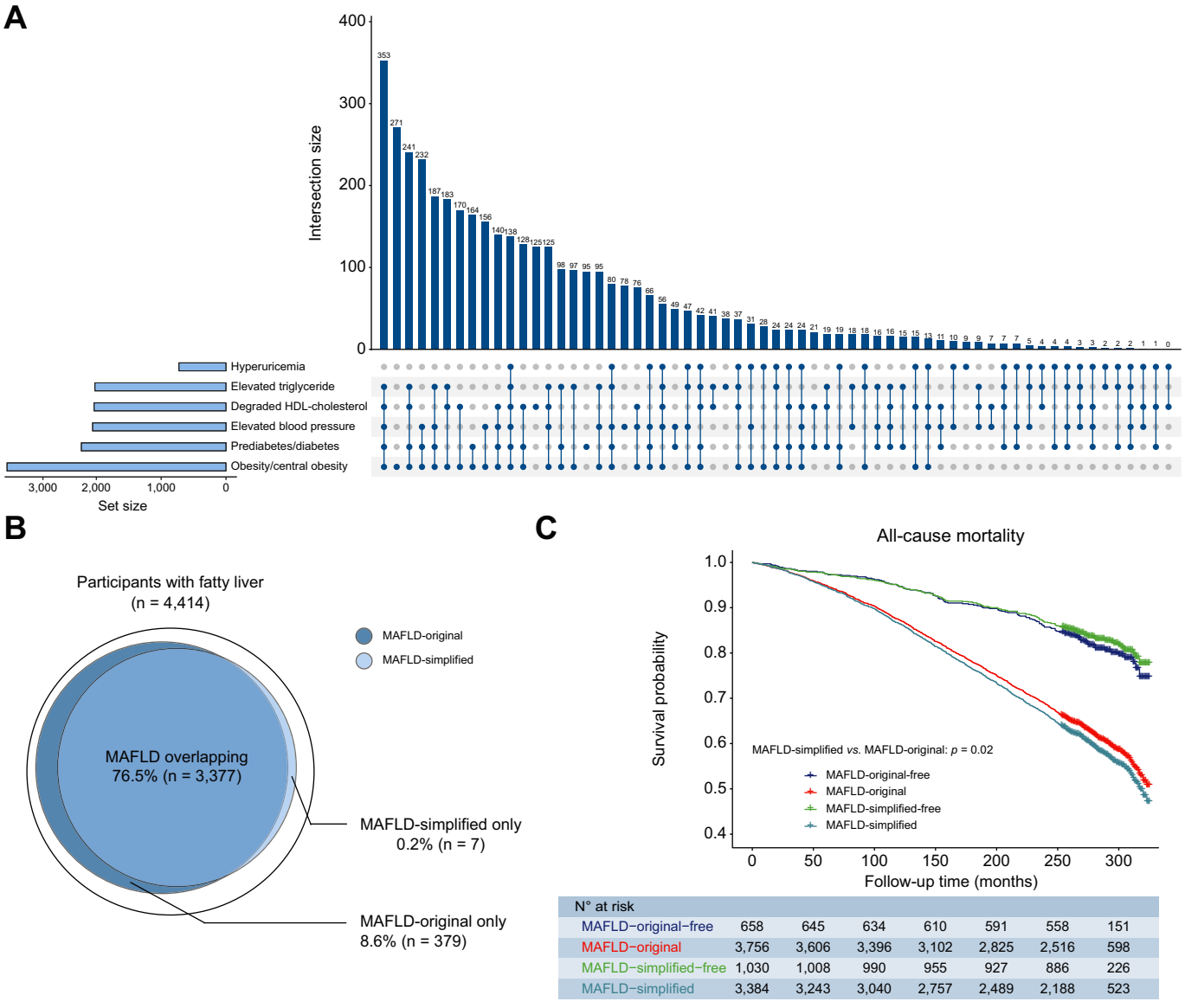
A simpler definition of MAFLD better predicts long-term all-cause mortality in American adults

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 from the United States. They also found that advanced fibrosis in MAFLD was associated with higher estimates for all-cause mortality than in non-alcoholic fatty liver disease (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 (T2DM), or evidence of metabolic dysregulation. Although MAFLD was



N° at risk							
MAFLD−original−free	658	645	634	610	591	558	151
MAFLD−original	3,756	3,606	3,396	3,102	2,825	2,516	598
MAFLD−simplified−free	1,030	1,008	990	955	927	886	226
MAFLD−simplified	3,384	3,243	3,040	2,757	2,489	2,188	523

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

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associated with an increased risk of all-cause mortality, some lean patients with MAFLD may not be at high risk of metabolism-related death. Besides, the MAFLD definition is complex and some subitems, such as HOMA-IR and high-sensitivity C-reactive protein, 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 simplified and more applicable set of criteria is 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 listing them as separate categories. Similarly, given that the majority of individuals with HOMA-IR scores ≥2.5 had at least 2 metabolic abnormalities (Fig. 1A), we did not list HOMA-IR score separately either. Besides, because high-sensitivity C-reactive protein, 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 2 of the following conditions: (i) obesity/central obesity: BMI ≥25 kg/m^2, 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 triglycerides: ≥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/dl 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 (Fig. 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 (Fig. 1B). Kaplan-Meier analysis confirmed that individuals with fatty liver 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: $p = 0.02$) (Fig. 1C). Compared with individuals who did meet the MAFLD-original criteria (MAFLD-original-free), the hazard ratio (HR) was 1.252 (95% CI 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 was 1.628 (95% CI 1.222–2.170) in MAFLD-simplified individuals, compared with MAFLD-simplified-free individuals ($p = 0.001$) (Fig. 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 individuals with fatty liver disease. The simplified diagnostic process may better identify high-risk individuals in clinical practice.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

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.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.01.015.

References

Author names in bold designate shared co-first authorship

[1] Kim D, Konyn P, Sandhu KK, Dennis BB, Cheung AC, Ahmed A. Metabolic dysfunction-associated fatty liver disease is associated with increased all-cause mortality in the United States. J Hepatol 2021;75(6):1284–1291.
[2] Eslam M, Newsome P, Sarin S, Anstee Q, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol 2020;73:202–209.
[3] Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. Series 1: programs and collection procedures. Vital Health Stat 1 1994:1–407.
[4] Blüher M. Metabolically healthy obesity. Endocr Rev 2020;41:405–420.
[5] Manco M, Bedogni G, Marcellini M, Devito R, Ciampalini P, Sartorelli MR, et al. Waist circumference correlates with liver fibrosis in children with non-alcoholic steatohepatitis. Gut 2008;57:1283–1287.
[6] **Foghsgaard S**, **Andreasen C**, Vedtofte L, Andersen ES, Bahne E, Strandberg C, et al. Nonalcoholic fatty liver disease is prevalent in women with prior gestational diabetes mellitus and independently associated with insulin resistance and waist circumference. Diabetes Care 2017;40:109–116.
[7] Shiha G, Alswat K, Al Khatry M, Sharara AI, Örmeci N, Waked I, et al. Nomenclature and definition of metabolic-associated fatty liver disease: a consensus from the Middle East and north Africa. Lancet Gastroenterol Hepatol 2021;6(1):57–64.

[8] **Ma Z**, **Xu C**, Kang X, Zhang S, Li H, Tao L, et al. Changing trajectories of serum uric acid and risk of non-alcoholic fatty liver disease: a prospective cohort study. J Transl Med 2020;18:133.
[9] Wijarnpreecha K, Panjawatanan P, Lekuthai N, Thongprayoon C, Cheungpasitporn W, Ungprasert P. Hyperuricaemia and risk of nonalcoholic fatty liver disease: a meta-analysis. Liver Int 2017;37:906–918.
[10] **Nobili V**, **Mosca A**, De Vito R, Raponi M, Scorletti E, Byrne CD. Liver zonation in children with non-alcoholic fatty liver disease: associations with dietary fructose and uric acid concentrations. Liver Int 2018;38:1102–1109.

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EFNA3 is a prognostic biomarker for the overall survival of patients with hepatocellular carcinoma

To the Editor:

We read with great interest the article by Husain *et al.*,[1] showing that the expression of *EFNA3* was upregulated in hepatocellular carcinoma (HCC) and related to poorer survival rates. Husain *et al.* found that the expression level of *EFNA3* was regulated by HIF-1α in a hypoxic microenvironment. Hypoxia-induced Ephrin-A3/EphA2 forward signaling played a vital role in initiation and progression of HCC. The authors identified the clinical significance and molecular mechanisms of *EFNA3* in HCC. However, the relationship between the HCC patients' overall survival (OS) and *EFNA3* was explored only based on The Cancer Genome Atlas (TCGA) database in their study. Without independent validation, evidence of the prognostic role of *EFNA3* in HCC is not solid. Hence, the clinical observations regarding the beneficial effects of *EFNA3* on OS in patients with HCC need to be confirmed in other independent cohorts.

Previous studies showed that *EFNA3* was a prognostic indicator of some types of tumors. For example, Zheng *et al.* demonstrated that upregulation of *EFNA3* was correlated with worse survival rates in gastric cancer.[2] Dent *et al.* showed that

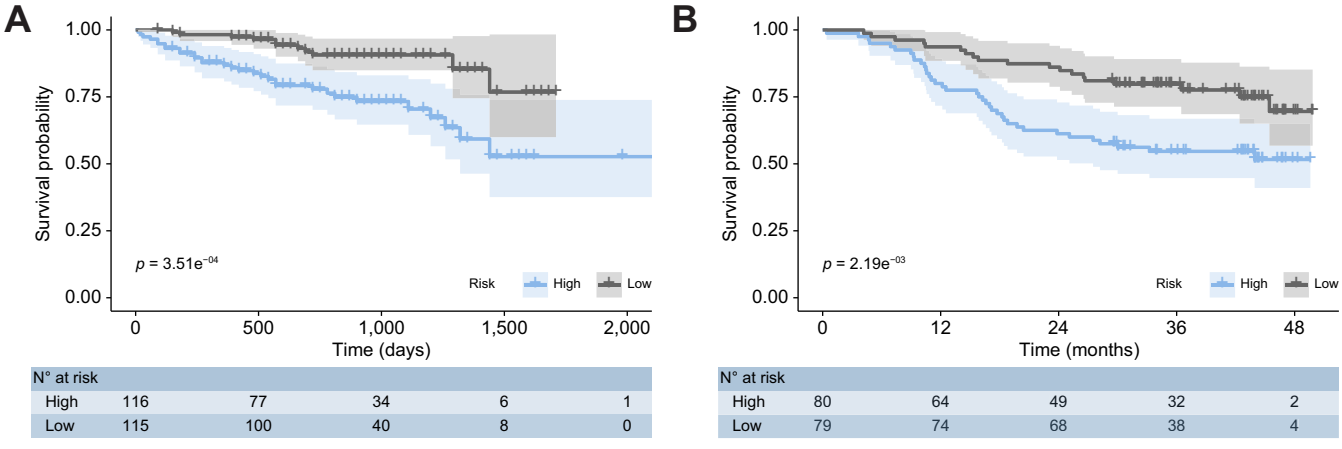

Fig. 1. Kaplan-Meier curves for overall survival based on gene expression of *EFNA3*. Log-rank test in (A) LIRI-JP and (B) CHCC cohorts.

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