JOURNAL OF HEPATOLOGY

Do we need a new cut-off for FIB-4 in the metabolic dysfunction-associated fatty liver disease era?

To the Editor:

We read the paper by Srivastava *et al.*[1] and the letter by Wu *et al.*[2] with great interest. As suggested by Wu *et al.*, the fibrosis-4 index (FIB-4) should be validated for application to the metabolic dysfunction-associated fatty liver disease (MAFLD) group. Wu *et al.* reported that the sensitivity of FIB-4 for the diagnosis of advanced fibrosis in patients with MAFLD was as low as 58% at a cut-off of 1.3, and only 75% at a cut-off of 1.0, in a biopsy-proven MAFLD cohort (n = 417). This finding indicates that there is a 25% to 42% risk of missing patients with advanced fibrosis. Moreover, the observed maximum negative predictive value (NPV) was only 80%. Therefore, Wu *et al.* insisted that the optimal FIB-4 cut-off value should be re-defined in MAFLD.

However, we offer another point of view. As the positive predictive value (PPV) and NPV are easily affected by disease prevalence, a validation of the diagnostic performance in a community cohort rather than patient cohort is desirable. Therefore, we evaluated FIB-4 for the diagnosis of advanced hepatic fibrosis in a community-based MAFLD cohort using magnetic resonance elastography (MRE).

The data of participants (n = 6,658) who have undergone MRE in 13 health check-up centres nationwide were included in our analysis. Non-alcoholic fatty liver disease (NAFLD) and MAFLD were defined based on the guidelines and a recent consensus-driven definition.[3,4] The definition of advanced hepatic fibrosis was based on the MRE standard of ≥3.6 kPa (range: 3.2~4.0 kPa). The sensitivity and NPV of the FIB-4 cut-off were set at 1.0[5] and 1.3 (2.0, age >65).[6]

Our findings showed that the age- and sex-adjusted prevalences of MAFLD and NAFLD were 33.9% and 28.7%, respectively. The AUROC of FIB-4 for advanced hepatic fibrosis was 0.80 (0.69–0.86) and 0.82 (0.71–0.86) in the MAFLD and NAFLD groups, respectively, which were not different between groups (Table 1). At a FIB-4 cut-off of 1.3 in the MAFLD group, the sensitivity, NPV, and accuracy for advanced hepatic fibrosis were 66.7% (50%–78%), 99.0% (96%–99%), and 77.9 (76%–77%), respectively. Moreover, the sensitivity, NPV, and accuracy were similar between the MAFLD and NAFLD groups. Although the diagnostic performance of FIB-4 in MAFLD was not different from that in the NAFLD population, the sensitivity for diagnosing advanced fibrosis was still low, at 66.7% (49%–78%), if a cut-off of 1.3 was used. This indicates that nearly one-third of patients with advanced fibrosis would be missed. When a cut-off of 1.0 was used, the sensitivity increased to 82.6% (69%–88%), and NPV was maintained at 99.2% (96%–99%). These findings are supported by the work of Shah *et al.*[5] They pointed out that the FIB-4 cut-off of 1.0 showed 100% sensitivity and 94.3% specificity in ruling out any fibrosis (F0 *vs.* F1–F4). Therefore, the optimal cut-off value of FIB-4 needs to be lower than 1.3 to appropriately screen patients with

Table 1. Diagnostic performance for advanced hepatic fibrosis defined by various FIB-4 cut-offs in patients with MAFLD or NAFLD.

Patients/FIB-4 cut-off	MRE cut-off (kPa)	Prevalence (%)	AUROC	*p* value	Accuracy (%)	Sen (%)	Spe (%)	PPV (%)	NPV (%)
MAFLD/1.0	3.2	6.17	0.69	<0.001	56.03	68.92	55.18	9.18	96.42
	3.4	3.97	0.733	<0.001	55.71	75.43	54.9	6.47	98.18
	3.6	2.4	0.801	<0.001	55.26	82.6	54.59	4.29	99.22
	3.8	1.91	0.818	<0.001	55.05	85.45	54.46	3.53	99.48
	4.0	1.46	0.855	<0.001	54.81	88.09	54.13	2.78	99.67
MAFLD/1.3 (2.0)†	3.2	6.17	0.69	<0.001	76.95	49.15	78.78	13.22	95.92
	3.4	3.97	0.733	<0.001	77.33	53.5	78.3	9.27	97.6
	3.6	2.4	0.801	<0.001	77.85	66.66	78.13	6.99	98.95
	3.8	1.91	0.818	<0.001	77.85	70.9	77.99	5.92	99.27
	4.0	1.46	0.855	<0.001	77.89	78.57	77.88	5.01	99.59
NAFLD/1.0	3.2	5.49	0.714	<0.001	56.55	74.61	55.5	8.89	97.4
	3.4	3.63	0.754	<0.001	56.13	81.39	55.18	6.41	98.74
	3.6	2.32	0.818	<0.001	55.58	87.27	54,82	4.4	99.45
	3.8	1.86	0.836	<0.001	55.28	88.63	54.65	3.57	99.6
	4.0	1.35	0.863	<0.001	54.94	90.62	54.46	2.65	99.74
NAFLD/1.3 (2.0)†	3.2	5.49	0.714	<0.001	77.75	52.3	79.23	12.78	96.61
	3.4	3.63	0.754	<0.001	78	56.97	78.79	9.21	97.98
	3.6	2.32	0.818	<0.001	78.38	69.09	78.6	7.14	99.07
	3.8	1.85	0.836	<0.001	78.52	75	78.59	6.2	99.4
	4.0	1.35	0.863	<0.001	78.34	81.25	78.3	4.88	99.67

IB-4, fibrosis-4 index; MAFLD, metabolic dysfunction-associated fatty liver disease; MRE, magnetic resonance elastography; NAFLD, non-alcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value; Sen, sensitivity; Spe, specificity. DeLong's test was used to compare the significance of AUROC of FIB-4 to reference line.

†A cut-off value of 2.0 was used when the patient's age was >65 years.

Received 25 May 2021; accepted 30 May 2021; available online 9 June 2021
https://doi.org/10.1016/j.jhep.2021.05.035

advanced fibrosis. The need to change the FIB-4 cut-off is not due to a change in the definition of MAFLD, but to increase the sensitivity of the screening strategy. It would be appropriate to lower the cut-off of FIB-4 to 1.0 so that it can be used as the first step in screening for advanced hepatic fibrosis among the general population.

In conclusion, the diagnostic performance of FIB-4 in the MAFLD group was not different from that in the NAFLD group. However, it would be appropriate to lower the cut-off to 1.0 in order to reduce the rate of missed advanced fibrosis diagnoses.

Financial support
The authors received no financial support to produce this manuscript.

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
Concept and design: D.W.J.; data collection and management: E.L.Y., S.C., N.E-H.; interpretation of data: D.W.J.; writing of the manuscript: H.P.; supervision: D.W.J. and N.E-H. All the authors approved the final version of the manuscript.

Patient consent
Informed consent was waived because of the retrospective nature of the study, and the analysis used anonymized clinical data.

Ethical approval
This study was approved by the Institutional Review Board of Hanyang University Hospital (IRB No. HY-2021-04-001).

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Author names in bold designate shared co-first authorship

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Huiyul Park[1,§]
Eileen L. Yoon[2,§]
Seon Cho[3]
Eun-Hee Nah[3,*]
Dae Won Jun[2,*]
[1]*Department of Family Medicine, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Republic of Korea*
[2]*Department of Internal Medicine, Hanyang University Hospital, Hanyang University College of Medicine, Republic of Korea*
[3]*Department of Laboratory Medicine, Health Promotion Research Institute, Seoul, Republic of Korea*
[*]Corresponding authors. Addresses: Department of Internal Medicine, Hanyang University College of Medicine, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Republic of Korea; Tel.: +82 2 2290 8338, fax: +82 2 972 0068.
[*]Health Promotion Research Institute, Korea Association of Health Promotion, 372, Hwagok-ro, Gangseo-gu, Seoul 07572, Republic of Korea; Tel.: +82-2- 2600-0107, fax: +82-2-2690-4915.
E-mail addresses: cellonah@hanmail.net, cellonah@kahp.or.kr (E.-H. Nah), noshin@hanyang.ac.kr (D.W. Jun)

§ Contributed equally to this work as co-first authors.

Population-specific cut-off points of fatty liver index for the diagnosis of hepatic steatosis

To the Editor:

Recently, metabolic dysfunction-associated fatty liver disease (MAFLD)[1] was proposed by an international panel of experts from 22 countries to replace non-alcoholic fatty liver disease (NAFLD). In this statement,[1] positive diagnostic criteria for MAFLD were proposed. In the diagnostic flowchart, the diagnosis of hepatic steatosis (HS) was the first step. Of the 3 methods highlighted for the diagnosis of HS, liver biopsy is the gold standard but invasive, abdominal ultrasonography is currently the most widely used first-line imaging technique,[2] and fatty liver index (FLI) is the only blood biomarker mentioned, but no specific cut-off points were given.

FLI is a simple algorithm developed by Bedogni *et al.*[3] for the prediction of fatty liver in the general population. It comprises 4 components: waist circumference (WC), body mass index (BMI), triglycerides, and gamma-glutamyltransferase (GGT). In Bedogni *et al.*'s paper,[3] gender was not found to be associated with fatty liver in final model. However, our preliminary study of 135,436 physical examination patients showed a significant difference in the optimal

Keywords: fatty liver index; cut-off points; hepatic steatosis.
Received 28 April 2021; received in revised form 16 May 2021; accepted 31 May 2021; available online 10 June 2021
https://doi.org/10.1016/j.jhep.2021.05.039