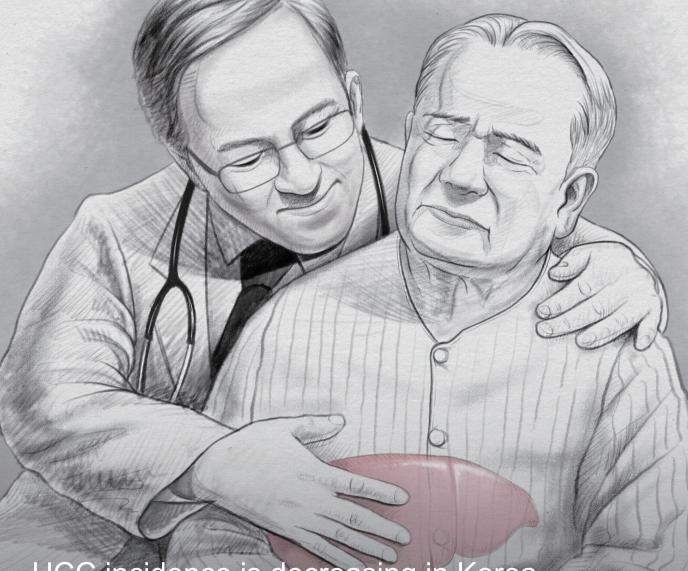# CLINICAL and MOLECULAR
HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases

HCC incidence is decreasing in Korea
but increasing in elderly

Early changes in biomarkers predict HBsAg response
Baveno-VII predicts decompensation in cACLD

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Correspondence

Correspondence on Editorial regarding "Screening and prediction of nonalcoholic fatty liver disease using a peripheral insulin resistance index: Potential benefits and limitations"

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Dear Editor,

We appreciate Drs. Soon Sun Kim and Jae Youn Cheong's valuable comments on our research determining predictive values of two insulin resistance (IR) indices, metabolic score for IR (METS-IR) and homeostatic assessment model for IR (HOMA-IR), for the prevalence and incidence of non-alcoholic fatty liver disease (NAFLD), published in *Clinical and Molecular Hepatology*.[1] We are happy to respond to the points they raised in their editorial letter.

The prevalence of NAFLD has steadily increased and is estimated to be approximately >50% by 2040.[2] As NAFLD is a risk factor for morbidities such as atherosclerotic cardiovascular disease or dementia,[3,4] many efforts to identify markers for early detection and prediction of NAFLD have been made. The association between NAFLD and metabolic dysfunction has been extensively investigated. The established risk factors for NAFLD include obesity, hypertriglyceridemia, metabolic syndrome, and diabetes mellitus.[5,6] Although these factors are closely related to peripheral IR,[7,8] a previous study has demonstrated that peripheral IR, not hepatic IR, correlates with hepatic fat.[9] Thus, we hypothesized that an index that reflects peripheral IR would also be appropriate for predicting the prevalence and incidence of NAFLD. The METS-IR demonstrated similar predictive power for the prevalence of NAFLD as HOMA-IR and superior predictive power for the incidence of NAFLD compared to HOMA-IR. These results may be due to the high METS-IR reflecting the presence of meta-

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bolic syndrome and/or diabetes mellitus. Although we used only the baseline METS-IR value in this study, the value of METS-IR changes with time. The longitudinal data of patients we encountered in clinical practice will provide useful information if the pattern of the METS-IR change with time is related to NAFLD. Therefore, we plan to verify the associations between METS-IR trajectories and incident NAFLD in a future study.

In a very recent study,[10] the predictive power for incident NAFLD of the METS-IR at 4 years in Chinese individuals without obesity was higher than that in our study (time-dependent area under the receiver-operating-curve [AUROC] in the Chinese study vs. our study, 0.752 vs. 0.683). Different ethnicities, short follow-up periods, and the use of abdominal ultrasonography to define NAFLD could have contributed to the discordance in the results between the two studies. Because abdominal ultrasonography was not performed in the Korean Genome and Epidemiology Study (KoGES), we used NAFLD-liver fat scores >−0.640 to define NAFLD in our study. In accordance with the editors' comments, we additionally performed the same analysis using a hepatic steatosis index (HSI) ≥36 to define NAFLD for validation. Among 8,360 participants with or without NAFLD at the baseline survey, 2,111 participants (25.3%) had NAFLD. The predictive powers of the METS-IR and HOMA-IR for the prevalence of NAFLD using HSI decreased compared to those of NAFLD using the NAFLD-liver fat score. In particular, the predictive power of the HOMA-IR decreased from 0.831 (0.821–0.842) to 0.544 (0.529–0.559), whereas that of METS-IR decreased from 0.831 (0.821–0.842) to 0.717 (0.705–0.730). Additionally, among 5,670 participants without NAFLD at the baseline survey, a total of 1,985 participants (35.0%) developed NAFLD during the 13.5-year follow-up period. The time-dependent AUROC for the incidence of NAFLD in HOMA-IR decreased from 0.551 (0.539–0.563) to 0.522 (0.514–0.530), whereas that of METS-IR decreased from 0.683 (0.671–0.695) to 0.575 (0.565–0.585).

Although both NAFLD-liver fat score and HSI are highly reliable markers for predicting NAFLD and NAFLD is closely related to IR,[11] the correlations of these two markers with the IR indices were heterogeneous in this study. Similarly, the correlation coefficient between the NAFLD-liver fat score and METS-IR (r1) was 0.499, and that between the HSI and HOMA-IR (r2) was 0.439, with significant differences between r1 and r2. While the correlation coefficient between the NAFLD-liver fat score and HOMA-IR (r3) was 0.650, the correlation coefficient between the HSI and HOMA-IR (r4) was only 0.078, with significant differences between r3 and r4. These results suggest a possible information bias. To determine a more precise result, defining NAFLD using imaging studies such as abdominal ultrasonography or abdominal computed tomography need to be considered in future studies.

In another study, we compared the predictive power of the METS-IR/triglyceride-glucose (TyG) index/HOMA-IR for advanced liver fibrosis in patients with NAFLD using the KoGES dataset.[12] The METS-IR had the highest predictive power for the prevalence of advanced liver fibrosis, followed by the TyG index and HOMA-IR. Although both the METS-IR and TyG index were significantly associated with incident advanced liver fibrosis in the crude model, the significant association with advanced liver fibrosis was maintained only in the METS-IR, not the TyG index, in the adjusted model. While the TyG index only reflects lipid profile, the METS-IR reflects both the lipid profile and obesity. The difference between these two IR indices made METS-IR better reflect malnutrition in patients with advanced liver disease, which may have caused METS-IR to have a significant association with advanced liver fibrosis in the adjusted model. Considering the inverse relationship between the METS-IR at baseline and incident advanced liver fibrosis in patients with NAFLD, improvement in the METS-IR does not always indicate an improvement in NAFLD. However, we cannot guarantee that changes in the METS-IR are also related to advanced liver fibrosis because both the lipid profile and body mass index fluctuate with time. Hence, determining whether the trajectories of different IR indices are associated with advanced liver fibrosis is necessary.

In conclusion, a high METS-IR can predict the prevalence and incidence of NAFLD. However, this does not always indicate that a low METS-IR score predicts improvement in NAFLD. Therefore, the current evidence for using METS-IR to monitor patients with NAFLD is insufficient. Follow-up studies should be performed to determine whether changes in

various IR indices over time are related to NAFLD and/or liver fibrosis.

Authors' contribution

Study concept and design: Jun-Hyuk Lee, Jee Hye Han, and Sang Bong Ahn; Data collection: Jun-Hyuk Lee, Kyongmin Park, Hye Sun Lee, and Hoon-Ki Park; Data analysis and interpretation: Jun-Hyuk Lee, Jee Hye Han, and Sang Bong Ahn; Manuscript writing: Jun-Hyuk Lee, Jee Hye Han, and Sang Bong Ahn. Final approval of the manuscript: All authors

Conflicts of Interest

The authors declare no conflicts of interest.

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