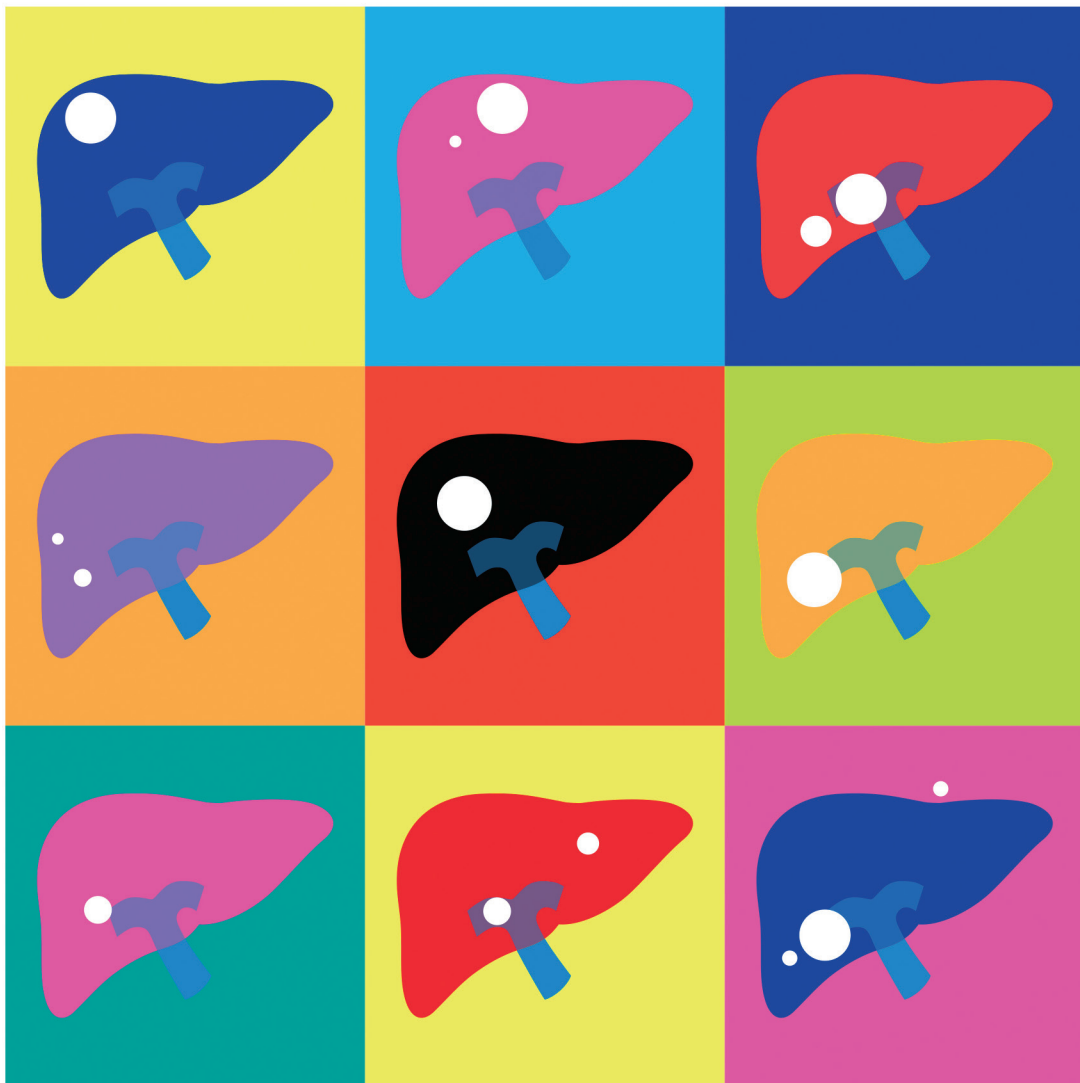# CLINICAL and MOLECULAR HEPATOLOGY

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Editorial

Screening and prediction of nonalcoholic fatty liver disease using a peripheral insulin resistance index: Potential benefits and limitations

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In a recent issue of *Clinical and Molecular Hepatology*, Lee et al.[1] reported the usefulness of the metabolic score for insulin resistance (METS-IR) in the screening and prediction of non-alcoholic fatty liver disease (NAFLD) in middle-aged and older Korean populations using Korean Genome and Epidemiology Study (KoGES) data. According to Lee et al.,[1] METS-IR, which is a marker for peripheral insulin resistance, has a similar predictive power for the prevalence of NAFLD; however, it shows a better predictive ability for incident NAFLD than that of the homeostatic model assessment for insulin resistance (HOMA-IR), a marker for hepatic insulin resistance, during the mean follow-up period of 13.6 years. Better predictability for developing incident NAFLD was consistently maintained in the subgroup analysis according to the presence of obesity or diabetes mellitus. Specifically, a METS-IR score higher than 35.7 was associated with incident NAFLD in subjects without NAFLD at baseline, while a score higher than 39.3 was associated with the presence of NAFLD in middle-aged and older (≥40 years old) Koreans. Given the increasing prevalence of

NAFLD in Korea,[2,3] this is a very timely study.

METS-IR is calculated using the following equation: Ln(2×fasting glucose [mg/dL]+fasting triglycerides [mg/dL]) ×body mass index/Ln(high-density lipoprotein cholesterol [mg/dL]).[4] This equation has three direct components (glucose, triglyceride, and high-density lipoprotein cholesterol levels) and one indirect component (body mass index) of metabolic syndrome. Even without circulating insulin levels in the equation, it can be validated using the euglycemic-hyperinsulinemic clamp data, frequently sampled in intravenous glucose tolerance test data, and a large cohort against the HOMA-IR. METS-IR is associated with prehypertension, hypertension, arterial stiffness, and incident ischemic heart disease.[5-10] A recent study reported the dose-response association of METS-IR with new-onset NAFLD in the non-obese Chinese population.[11] The risk of incident NAFLD increased progressively with the METS-IR (Q1: reference; Q2: hazard ratio [HR], 2.69; 95% confidence interval [CI], 1.87–3.86; Q3: HR, 4.25; 95% CI, 2.86–6.30; Q4: HR, 6.40; 95% CI, 4.06–10.08, *P*<0.001). According to the results of the studies published thus far, MET-IR is a good method for the screening or prediction of diseases related to metabolic syndrome. Given the

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factors used for its calculation, METS-IR may not be a novel marker, but rather a score of appropriately remodeled variables of metabolic syndrome. However, considering the ease of measuring the factors used in this formula, it can be used as a screening or predictive tool for NAFLD in clinical practice. Meanwhile, the authors of this study have published an article on the association between METS-IR and advanced liver fibrosis.[12] The authors compared the predictability of liver fibrosis of METS-IR, HOMA-IR, and triglyceride-glucose index using the same KoGES data. The areas under the receiver operating characteristic curve for predicting advanced liver fibrosis of the METS-IR was 0.744 (95% CI, 0.679–0.810), significantly higher than those of triglyceride-glucose index and HOMA-IR (0.644 and 0.633, respectively). Interestingly, subjects with the highest tertile of METS-IR (≥45.71) showed a significant low risk for incident advanced liver fibrosis compared with those with the lowest tertile (adjusted HR, 0.59; 95% CI, 0.37–0.94; P=0.026). METS-IR is deemed to be more predictive of liver fibrosis than HOMA-IR because it reflects the lipid profile. Considering malnutrition in subjects with advanced liver disease,[13,14] triglyceride content and body mass index of METS-IR equation can be affected.

Healthcare big data available in South Korea include the Korea National Health and Nutrition Examination Survey (KNHANES), the Korean National Health Insurance Service (KNHIS), the Korean Health Insurance Review and Assessment Service (HIRA), and the KoGES data. First, KNHANES is a nationally representative cross-sectional survey that includes approximately 10,000 individuals each year and collects information on socioeconomic status, health-related behaviors, quality of life, healthcare utilization, anthropometric measures, biochemical and clinical profiles for non-communicable diseases and dietary intakes.[15,16] The disadvantage of KNHANES is that cohort study is not possible due to its nature as cross-sectional survey. In addition, there is no information on the disease diagnosis code and drug prescription code. Lack of information on imaging tests such as abdominal ultrasonography, computed tomography, bilirubin, alkaline phosphatase, gamma glutamyl transpeptidase, serum albumin, prothrombin time is another limitation for liver disease

study. Next, KNHIS and HIRA are representative claim database of South Korea. The Korean government introduced mandatory social health insurance for industrial workers in large corporations in 1977 and extended it incrementally to the self-employed until it covered the entire population in 1989. In 2000, all insurance societies were merged into one single-payer.[17] Data are collected into the KNHIS and HIRA database when Korean clinics or hospitals submit an insurance claim to the National Health Corporation for their medical services to be reimbursed. Both datasets have the advantage of including disease code, drug prescription information, and medical cost information, on the other hand, have the disadvantage of not providing radiologic study or blood test results. However, KNHIS can provide information on the results of national health examinations and the date and cause of death in a limited situation.[18] Lastly, the Korea Disease Control and Prevention agency started a large-scale cohort project called KoGES in 2001 to investigate the genetic and environmental factors related to chronic diseases such as diabetes, hypertension, obesity, metabolic syndrome, and cardiovascular disease. The Anseong-Ansan cohort, a part of KoGES, is a representative community-based cohort.[19] This cohort is suitable for a longitudinal study to evaluate the causal relationship and also included health-related behaviors, anthropometric measures, and biochemical and clinical profiles. Unfortunately, information on abdominal ultrasonography is lacking, therefore, the definition of NAFLD has to depend on blood tests as in this study. Considering KoGES is the only longitudinal cohort which includes insulin level, KoGES was an excellent choice for the purpose of this study.

The limitation of the study by Lee et al.[1] is that the predictive power of METS-IR was not as high as expected (Heagerty's integrated area under the curve, 0.683). In the Chinese study, the area under the curve of METS-IR for incident NAFLD at 1, 2, 3, and 4 years was 0.784, 0.756, 0.758, and 0.752, respectively.[11] This discordance was partly due to the difference in the duration of the two studies (mean, 13.6 years vs. median, 2.2 years). The two main reasons for its modest predictive power are that other factors may play a role in the occurrence of NAFLD and that METS-IR may fluc-

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Abbreviations:

CI, confidence interval; HIRA, Health Insurance Review and Assessment Service; HOMA-IR, homeostatic model assessment for insulin resistance; HR, hazard ratio; KNHANES, Korea National Health and Nutrition Examination Survey; KNHIS, Korean National Health Insurance Service; KoGES, Korean Genome and Epidemiology Study; METS-IR, metabolic score for insulin resistance; NAFLD, nonalcoholic fatty liver disease

tuate with time. Further research is needed to determine how to interpret the METS-IR changes during the follow-up period. As mentioned earlier, the authors reported an inverse relationship between METS-IR and hepatic fibrosis; that is, subjects with advanced liver fibrosis defined by the fibrosis-4 index showed low METS-IR.[12] Therefore, careful interpretation of METS-IR changes is warranted as improvement in METS-IR does not always indicate an improvement in NAFLD. Another limitation is that ultrasonography or liver biopsy was not performed in this study. NAFLD was defined only with NAFLD-liver fat score.[20] Given the limitation of KoGES dataset, analyses using hepatic steatosis index or fatty liver index may be necessary for the validation.

Authors' contribution

S.S.K drafted the manuscript and J.Y.C revised and finalized the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.

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