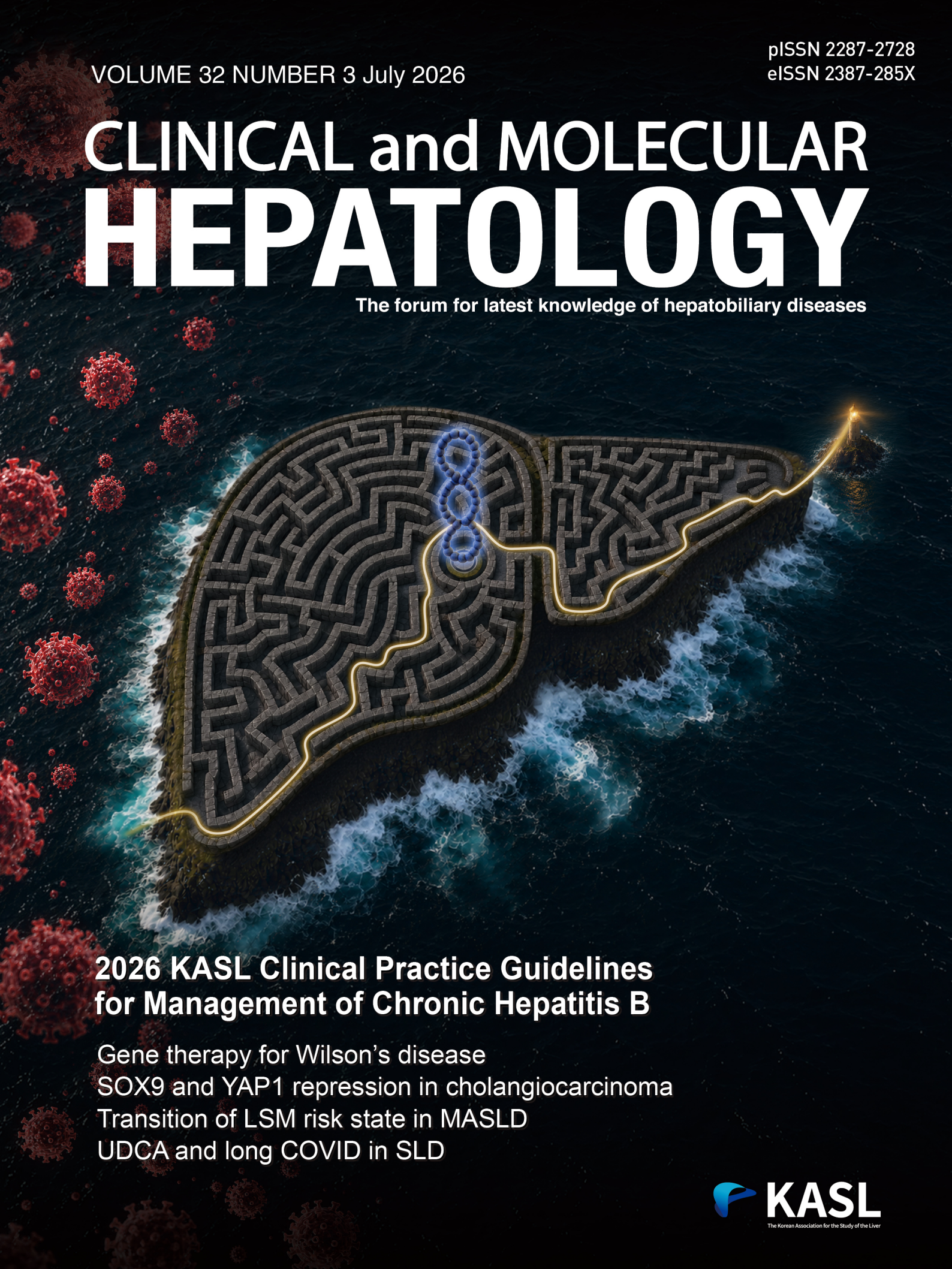


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Correspondence

The lean phenotype in metabolic dysfunction-associated steatotic liver disease: diagnostic challenges and prognostic implications: Correspondence to editorial on “Normal-weight metabolic dysfunction-associated steatotic liver disease: reclassification, characteristics, and adverse liver outcomes across diverse populations”

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Keywords: Steatotic liver disease; Body mass index; Waist circumference; Fibrosis-4 index

Dear Editor,

We thanked Kim et al. for their insightful editorial entitled “Rethinking lean metabolic dysfunction-associated steatotic liver disease: unrecognized risk in lean populations”^{1,2}. Their work clarifies the complexity of the “lean phenotype” and highlights potential bias in disease burden estimates during the conceptual shift from nonalcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated steatotic liver disease (MASLD). This underscores our conclusion that caution is required when applying historical data based

on lean NAFLD to the current lean MASLD, as the transition results in incomplete overlap between the two populations, especially in community settings. We fully acknowledge the authors’ critical concerns regarding the lean phenotype within the steatotic liver disease (SLD) spectrum and would like to take this opportunity to respond.

The editorial correctly notes that lean NAFLD actually comprises distinct subgroups, including metabolically healthy individuals with incidental SLD (cryptogenic SLD), centrally obese but normal-body mass index (BMI) patients at high cardiometabolic risk, and severely ill individuals

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who lost weight. To accurately estimate the risk of all-cause mortality in this heterogeneous population, we adjusted for confounding factors such as age and extrahepatic diseases in our analyses. Nevertheless, unmeasured confounders could still exist and multivariable adjustment could not account for the impact of residual confounding. Nevertheless, our results align with other studies,³ indicating the “obesity paradox” phenomenon as observed in other chronic diseases.⁴

We appreciate the authors’ insights extending from this phenomenon. Specifically, there is a subset within the normal-weight MASLD population who present with central obesity, sarcopenia, or systemic illness. This distinct phenotype is intrinsically linked to insulin resistance and metabolic dysfunction⁵ that significantly elevates mortality risk. Therefore, the validation of non-invasive tests for fibrosis detection and risk stratification is crucial in this specific subgroup. Given that transient elastography is likely to be accurate in lean individuals due to the absence of excess percutaneous fat,⁶ the observed discrepancy between FIB-4 and fibrosis by histology or transient elastography may be more attributable to the limited accuracy of FIB-4 for this unique cohort.

Furthermore, BMI alone may be an inadequate triage tool to differentiate MASLD phenotypes, as it is unable to distinguish between percutaneous and abdominal adiposity. Acknowledging this, the *Lancet Diabetes & Endocrinology* Commission defined “clinical obesity” as a chronic, systemic illness due to excess adiposity, requiring confirmation either via direct body fat measurement or anthropometric waist-centered criteria in addition to BMI.⁷ Evidence from nationwide cohorts suggests waist-based measures correlate more closely with hepatic steatosis and fibrosis, providing a superior prognostic value in MASLD.⁸ Future studies are warranted to characterize the long-term impact of body composition on outcomes, and appropriate measurements to establish objective phenotype classifications for MASLD.

In summary, the editorial by Kim et al. effectively summarizes our major findings while raising critical points regarding the distinct subgroups embedded in the lean NAFLD,

the potentially limited utility of non-invasive tests, and the significance of waist-based measures in defining lean and non-lean phenotypes. Lean MASLD should be treated as a distinct clinical target requiring optimized definition strategies and potentially, phenotype-specific management.

Authors’ contribution

The authors contributed equally to the literature review and drafting of the manuscript. They all approved the final version of the manuscript.

Conflicts of Interest

Song SJ and Jun DW had no conflicts of interest to declare. Terry Yip has served as an advisory committee member for Gilead Sciences and GSK, and a speaker for Gilead Sciences. He has received a research grant from Gilead Sciences. Vincent Wong served as a consultant or advisor for AbbVie, AstraZeneca, Boehringer Ingelheim, Echosens, Eli Lilly, Gilead Sciences, Merck, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and TARGET PharmaSolutions; a speaker for Abbott, AbbVie, AstraZeneca, Echosens, Gilead Sciences, and Novo Nordisk; an independent non-executive director for Furui; and a co-founder of Illuminatio Medical Technology. He has received a research grant from Gilead Sciences.

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Abbreviations:

BMI, body mass index; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; SLD, steatotic liver disease

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