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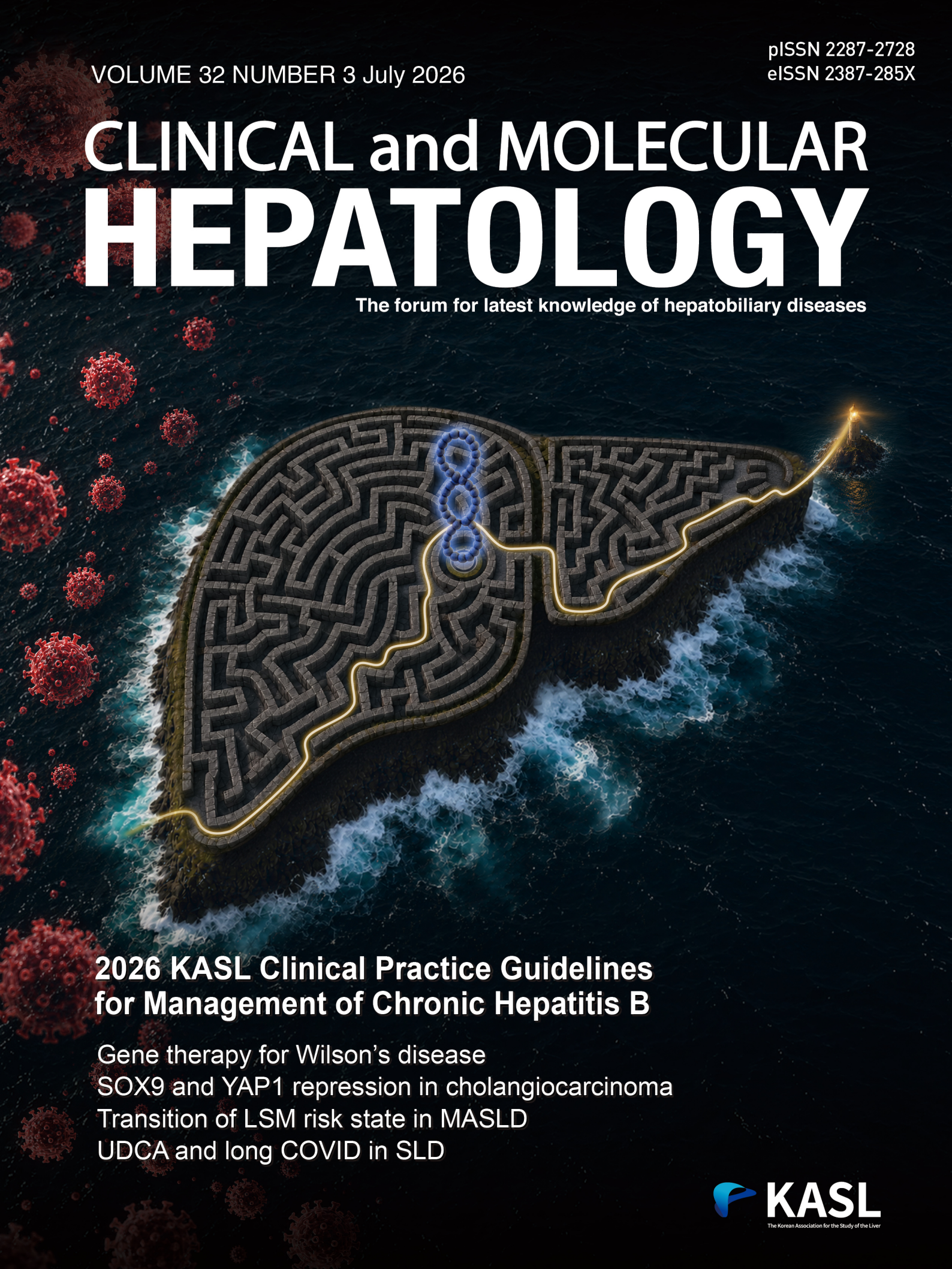

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Editorial

Rethinking lean metabolic dysfunction-associated steatotic liver disease: Unrecognized risk in lean populations: Editorial on "Normal-weight metabolic dysfunction-associated steatotic liver disease: Reclassification, characteristics, and adverse liver outcomes across diverse populations"

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease in the world.[1] In the United States, the contemporary prevalence of steatotic liver disease (SLD) is 35.0%, with 31.9% having MASLD during 2017 to 2023.[2] Notably, MASLD-related mortality steadily increased before the coronavirus disease 2019 (COVID-19) pandemic and then accelerated during the early pandemic in the United States.[3,4] The shift from non-alcoholic fatty liver disease (NAFLD) to MASLD aimed to focus on metabolic dysfunction as the primary driver of SLD.[5] However, the lean (or normal-weight) population may expose shortcomings in this new framework, given that several individuals previously categorized as having lean NAFLD might no longer fulfill the criteria for lean MASLD.

In a large, multi-cohort study from Hong Kong (HK), South Korea, and the United States, Song et al.[6] show that a considerable proportion of lean NAFLD falls outside the current MASLD definition. This study points out that there is a more refined risk assessment in lean populations who do not fit the usual obesity-centered model. The central conceptual shift from NAFLD to MASLD is the addition of a requirement for at least one cardiometabolic risk factor (CMRF) in the presence of SLD, moving from a diagnosis of exclusion to one explicitly defined by underlying metabolic dysfunction. For overweight or obese individuals with NAFLD, this change has little practical effect, because elevated body mass index (BMI) alone fulfills CMRF criteria and brings almost all such patients under the umbrella of MASLD. By contrast, the normal-weight group is markedly

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reshaped, with 9.0–26.7% of community-based NAFLD patients lacking any CMRF and consequently being reclassified as "cryptogenic SLD" rather than MASLD under the new terminology. Estimates of disease burden and widely used risk prediction models may be largely based on NAFLD cohorts that included these lean, metabolically healthy populations. Excluding them from MASLD risks underpresenting the full spectrum of SLD and complicates longitudinal comparisons over time. The authors' cross-cohort analyses show near-complete overlap between NAFLD and MASLD in overweight and obese groups but marked divergence in normal-weight community cohorts, quantifying the extent to which lean NAFLD falls outside the current MASLD framework.

A United States national study estimated that lean MASLD had a prevalence of 9.3% (95% confidence interval [CI], 7.0–11.6), corresponding to about 4.2 million of the approximately 52.3 million lean adults.[7] Among those with lean MASLD, advanced fibrosis and cirrhosis were presented in 2.4% (95% CI, 1.1–5.3) and 2.0% (95% CI, 0.8–4.7), respectively.[7] Notably, the prevalence of advanced fibrosis was comparable between lean and overweight/obese populations in the HK biopsy cohort, the HK magnetic resonance spectroscopy (MRS) cohort, and the Korean magnetic resonance elastography (MRE) cohort, consistent with a previous study.[8] Another intriguing finding is the discordance between liver-related events (LREs) and all-cause mortality across BMI categories. In the HK Clinical Data Analysis and Reporting System (CDARS) cohort with longitudinal outcomes, individuals with normal-weight MASLD exhibited a comparable incidence of LREs to those who were overweight or obese (2.81 vs. 2.59 per 1,000 person-years). But patients with normal-weight MASLD had a higher all-cause mortality than those with overweight or obese MASLD (23.44 vs. 13.80 per 1,000 person-years). Multi-variable analyses consistently showed that overweight and obese MASLD had a lower all-cause mortality risk than normal-weight MASLD, even after adjusting for CMRFs, Fibrosis-4 index (FIB-4), and extrahepatic comorbidities and applying 2-year lag analyses to reduce reverse causation. The results mirror the "obesity paradox" observed in other chronic diseases, where higher BMI is sometimes associated with better survival once the disease is established.[9] A recent systematic review also found higher all-cause mortality in lean MASLD compared to non-lean MASLD, with a pooled hazard ratio of 1.43 (95% CI, 1.15–1.77).[10] In Song et al.'s study,[6] normal-weight MASLD patients tended to be older and had a greater burden of non-hepatic comorbidities such as stroke and chronic kidney disease. Taken together, these findings suggest a subset of the normal-weight MASLD population may have central obesity, sarcopenia, or systemic illness, making non-hepatic factors the determinants of prognosis. This highlights that lean MASLD should not be regarded as low risk and that BMI alone is an inadequate triage tool.[11] The clinical implications are considerable. First, the data argue strongly against using BMI-based definitions that underestimate risk in normal-weight individuals with MASLD, particularly in populations with a high prevalence of cardiometabolic disease. Clinicians should emphasize waist-based measures (such as waist circumference, sagittal abdominal diameter, etc.), detailed CMRF profiling, and careful fibrosis assessment. Second, the mismatch between FIB-4 and fibrosis by histology or transient elastography in lean populations points to the limitations of commonly used noninvasive scores in community settings as well as the possibility for misclassification if FIB-4 is applied without context. For researchers, the transition from lean NAFLD to lean MASLD complicates the interpretation. This study indicates that older NAFLD cohorts should not be simply re-labeled as MASLD cohorts, particularly in lean populations where roughly one quarter of community NAFLD might not meet MASLD criteria.

A key strength of the current work is the inclusion of multi-ethnic cohorts and a mix of hospital, community, and health check-up settings. However, the authors appropriately note that longitudinal outcome data are largely driven by the HK CDARS cohort and that prospective Western data on normal-weight MASLD remain scarce. Overall, this evidence supports viewing SLD as a continuum of phenotypes rather

Abbreviations:

BMI, body mass index; CDARS, Clinical Data Analysis and Reporting System; CI, confidence interval; CMRF, cardiometabolic risk factor; COVID-19, coronavirus disease 2019; FIB-4, Fibrosis-4 index; HK, Hong Kong; LRE, liver-related event; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; MRS, magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; SLD, steatotic liver disease

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than a single entity defined by BMI or a binary cardiometabolic cutoff. Specifically, lean NAFLD likely encompasses at least three overlapping subgroups: genuinely metabolically healthy individuals with incidental SLD; centrally obese but BMI-normal patients at high cardiometabolic risk; and frail or comorbid individuals in whom low or declining weight reflects systemic illness. Future classification schemes may need to look beyond the simple presence or absence of CMRFs to incorporate body composition, sarcopenia, central adiposity, and the burden of extrahepatic disease.

For now, the key message for clinicians and health policymakers is that while the move from NAFLD to MASLD clarifies disease constructs for many patients, it creates important blind spots in the lean population. Song and colleagues provide a strong, multi-ethnic quantification of this gap and a timely alert that lean MASLD demands the same vigilance as its obesity-associated counterpart.[6] Rather than assuming that a change in terminology will resolve previous shortcomings, the field should treat lean MASLD as a priority target for optimized diagnostic strategies, mechanistic studies, and customized therapies.

Authors' contribution

Donghee Kim and Aijaz Ahmed were responsible for the study concept and design, interpretation and presentation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and approval of the final draft manuscript. Anoushka Shenoy was responsible for the interpretation and presentation of data, critical revision of the manuscript for important intellectual content, and approval of the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest in preparing this manuscript, including financial and/or material support.

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