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Editorial

Rethinking first-line screening in MASLD beyond the limitations of Fibrosis-4 index: Editorial on “Risk stratification by noninvasive tests in patients with metabolic dysfunction-associated steatotic liver disease”

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Noninvasive tests (NITs) have rapidly evolved as critical tools in the assessment of patients with metabolic dysfunction-associated steatotic liver disease (MASLD), which affects more than 27.5% of the adult population in South Korea.¹ In this context, the study by Lee et al. offers a valuable contribution by validating the Korean Association for the Study of the Liver (KASL) two-step approach in a real-world Korean cohort.^{2,3}

The KASL approach, which relies on an initial fibrosis-4 (FIB-4) index followed by vibration-controlled transient elastography, effectively stratified over 8,000 patients with MASLD into four risk categories. The clear gradient in liver-related event (LRE) incidence—from 0.35% at 5 years in the low-risk group to 5.46% in the high-risk group—confirms the algorithm’s prognostic relevance. Furthermore, the simplified three-tier classification enhances its clinical

utility, particularly in primary care, without compromising predictive performance. This study is notable for its robust sample size, long-term follow-up, and direct comparison with other prominent models such as the AGA algorithm and FIB-4 combinations with Agile or FibroScan-Aspartate Aminotransferase scores.^{4,5} Notably, despite its simplicity, the predictive accuracy of the KASL method was comparable to more complex models, underscoring its practicality. In particular, the high negative predictive value (>99%) observed across timepoints emphasizes its strength in safely ruling out patients at low risk of LRE.

Several key messages emerge from this study. First, NIT-based risk stratification can be confidently integrated into clinical workflows, enabling timely surveillance and referrals. Second, while advanced scores like Agile 3+ may offer greater discriminatory power in select populations, their complexity may hinder routine use. Third, serial assessment—tracking changes in fibrosis or stiffness over time—may further refine prognosis beyond baseline values alone.

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Despite the strengths, several limitations should be considered when interpreting the clinical implications. First, the retrospective design and relatively short follow-up period limit the ability to infer causality or monitor disease progression dynamically. More importantly, the overall incidence of LREs was low, and only 9.0% of patients were classified as high-risk, raising concerns about whether the cohort was sufficiently enriched with high-risk individuals to robustly validate the stratification framework.

Second, the distinction between intermediate-low and intermediate-high risk groups was based on an arbitrary combination of FIB-4 and liver stiffness thresholds, lacking clear biological justification or external validation. Although the KASL MASLD guideline references the referral pathway from the KASL NIT guideline, it does not explicitly endorse four-group stratification.⁶ Thus, the four-tier classification appears to be constructed post hoc. In particular, the creation of the intermediate-low group may reflect the well-known diagnostic limitations of FIB-4 in borderline ranges rather than a truly distinct biological risk category. This issue is further underscored by the authors' own use of a simplified classification, which consolidates the four original groups into three.

Third, the diagnostic performance of FIB-4 is particularly limited in patients with type 2 diabetes mellitus (T2DM), who are at higher risk for advanced fibrosis. A recent East Asian multicenter study by Kim et al. involving 1,906 biopsy-confirmed MASLD patients demonstrated a significantly lower area under the curve (AUC) for FIB-4 in T2DM patients compared to non-T2DM patients (0.761 vs. 0.821, $P=0.044$), suggesting that diabetes attenuates the discriminatory power of FIB-4.⁷ This is particularly relevant given that approximately one-third of the cohort in the current study had T2DM. The KASL algorithm applies uniform FIB-4 thresholds regardless of metabolic phenotype, which may lead to performance overestimation in diabetic patients.

Although the accessibility and ease of FIB-4 make it an appealing first-line tool, caution is warranted when applying it to younger individuals and those with T2DM. Efforts to

address these limitations are ongoing. A recent head-to-head comparison of ten NITs by Van Kleef et al., using data from the Rotterdam Study and NHANES, showed that the Metabolic dysfunction-associated fibrosis score (MAF-5) consistently outperformed FIB-4 across key outcomes—including liver stiffness ≥ 8 kPa, advanced fibrosis, and MASH—with AUCs up to 0.93.⁸ Notably, in individuals aged 18–35, FIB-4 sensitivity fell below 10%, while MAF-5 retained a sensitivity of 71%, underscoring a substantial performance gap in younger adults at high metabolic risk. These findings highlight that while FIB-4 remains a pragmatic starting point, its limitations are increasingly evident in the very populations that would benefit most from early intervention.

Future algorithms should adopt a more tailored approach by integrating metabolic phenotype, age, and adjunctive biomarkers into MASLD risk assessment. Risk stratification cutoffs should be anchored in externally validated outcomes, and continuous fibrosis markers may enhance discrimination. Prospective, event-enriched studies are essential to validate each risk category and support the development of dynamic models incorporating longitudinal fibrotic changes.

In conclusion, this study provides compelling validation of the KASL two-step approach as a practical and scalable framework for MASLD evaluation. However, it also highlights important limitations of the FIB-4 index. Personalized adaptation of screening strategies—guided by comorbidities, demographics, and adjunctive tools—may be essential to optimize risk stratification and improve clinical outcomes in patients with MASLD.

Authors' contributions

Conception or design of the work: H.A. Lee; Drafting the article: Y.Y. Cho and H.J. Kim; Critical revision of the article: H.A. Lee; Final approval of the version to be published: H.J. Kim.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Abbreviations:

AUC, area under the curve; FAST, FibroScan-Aspartate Aminotransferase; FIB-4, fibrosis-4; KASL, Korean Association for the Study of the Liver; LRE, liver-related event; MAF, Metabolic dysfunction-associated fibrosis score; MASLD, metabolic dysfunction-associated steatotic liver disease; NIT, noninvasive tests; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography

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