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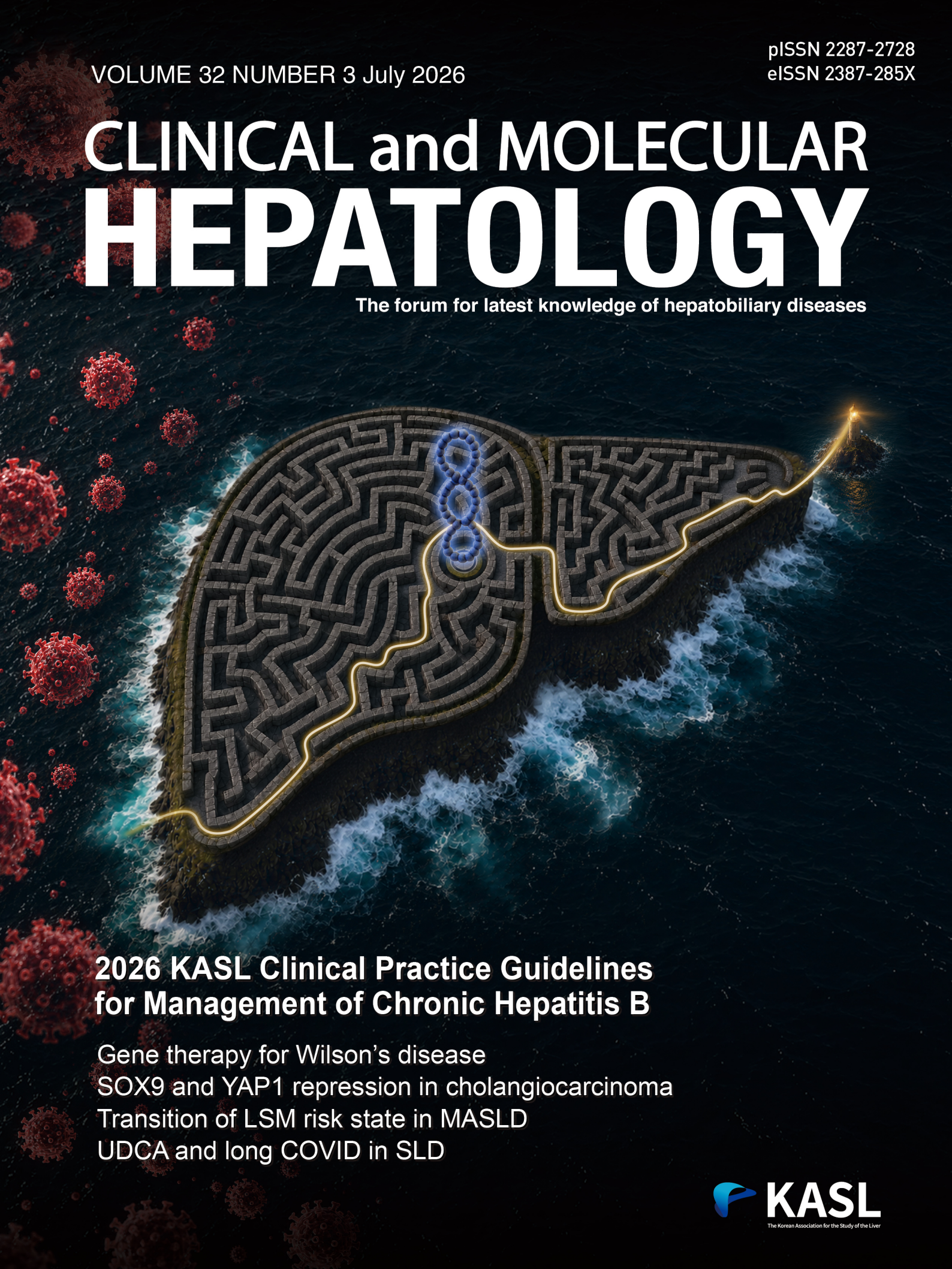

2026 KASL Clinical Practice Guidelines for Management of Chronic Hepatitis B

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Letter to the Editor

Discordant FIB-4 and liver stiffness in metabolic dysfunction-associated steatotic liver disease: Toward clinically coherent risk stratification: Letter to the Editor on "Histological severity and hepatic outcomes in patients with metabolic dysfunction-associated steatotic liver disease and discrepant FIB-4 and liver stiffness measurement"

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Keywords: MASLD; FIB-4; Liver stiffness

Dear Editor,

We read with great interest the multicenter study by Rabbat et al.[1] evaluating histological severity and liver-related outcomes among patients with metabolic dysfunction-associated steatotic liver disease (MASLD) with concordant versus discrepant noninvasive assessments (Fibrosis-4 index [FIB-4] and vibration-controlled transient elastography [VCTE]-derived liver stiffness). The authors address a common and clinically consequential scenario (discordant risk classification) and provide important data that will inform contemporary pathways based on sequential testing. We would like to offer three comments that may further strengthen the clinical interpretability and implementation of these findings.

First, the clinical interpretation of discordance may be incomplete if it remains confined to liver-related endpoints, even when competing–risk methods are used. While the competing–risk framework appropriately treats non-liver–related death as a competing event when estimating the in-

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cidence of liver-related events (LREs), the clinical message that readers may take home still hinges largely on hepatic outcomes. This is potentially problematic in MASLD, where overall prognosis is often driven by cardiovascular disease and extrahepatic malignancy rather than liver complications alone.[2,3] In particular, the phenotype characterized by elevated FIB-4 but relatively low liver stiffness could plausibly reflect systemic vulnerability (age-related risk, inflammatory activity, thrombocytopenia, frailty, or broader cardiometabolic burden) rather than a predominantly hepatic signal.[4] Indeed, elevated FIB-4 has been shown to independently predict cardiovascular disease and all-cause mortality, suggesting that high FIB-4 with low liver stiffness measurement (LSM) may reflect systemic vulnerability rather than purely hepatic pathology.[5] Recent studies also demonstrate that FIB-4 is associated with subclinical cardiovascular disease progression, reinforcing its role as a marker of overall cardiometabolic risk.[6] Under such circumstances, a comparatively low or non-significant association with LREs should not be interpreted as "low risk" in a broader clinical sense; it may simply indicate that competing causes of death occur earlier or more frequently. From this perspective, the discordant strata may represent distinct risk profiles with implications that extend beyond hepatology-focused pathways. A brief characterization of non-liver-related mortality across the discordant/concordant groups would therefore help prevent over-narrow interpretation, with any additional breakdown by cardiovascular versus malignancy-related deaths serving mainly to contextualize the phenotype rather than to redefine the study's primary conclusions.

Second, the current presentation may be difficult to act on in practice because it does not clearly communicate absolute risk over clinically relevant time horizons. Although the study reports robust relative associations and incidence rates, clinicians typically need answers framed as: "In this group, how many LREs should I expect over the next 3–5 years?" and "Is that high enough to justify referral, additional testing, or intensified surveillance?" This is particularly relevant for discordant profiles, where the key decision is whether the absolute risk is sufficiently elevated to warrant escalation (e.g., hepatology referral, evaluation for portal hypertension, or closer monitoring), rather than whether the relative risk differs from the low-low group.[4] When absolute risk remains low, even a several-fold increase may still translate into very few events and would argue for a conservative, stepwise approach; conversely, a modest relative increase could be important if the baseline risk is already substantial. Presenting simple, time-specific cumulative incidence estimates (e.g., 3- and 5-year) alongside absolute risk differences across the four strata would therefore make the findings directly interpretable at the bedside, and a brief conversion to "events per 1,000 patients" could further support implementation across settings with different resources.

Third, differences in follow-up care and treatment during the observation period could partly shape the observed gradients in hepatic outcomes, and this deserves brief clarification. In routine MASLD care, patients do not remain "untreated" after baseline testing. Weight loss efforts (including bariatric procedures), initiation or escalation of glucose-lowering therapies (such as GLP-1 receptor agonists or SGLT2 inhibitors), statin use, and tighter blood pressure control may occur during follow-up, and these changes can influence liver stiffness, metabolic risk, and ultimately hepatic outcomes.[7,8] At the same time, a discordant or high-risk non-invasive profile may prompt more frequent visits, imaging, or endoscopic assessment, which could increase the likelihood of detecting outcomes, particularly hepatocellular carcinoma, compared with patients who are followed less intensively.[9] Because the primary models mainly adjust for baseline characteristics, it remains unclear to what extent the observed differences across strata reflect underlying disease biology versus differences in subsequent management and surveillance intensity.[10] The lack of longitudinal treatment data limits the interpretation of the findings of Rabbat et al.[1] Future studies that incorporate treatment histories and management changes (e.g., weight loss, initiation of cardiometabolic therapies, or variations in surveillance frequency) will provide valuable insights into how these factors influence disease progression and competing mortality. A short description of major management

Abbreviations:

FIB-4, Fibrosis-4 index; LREs, liver-related events; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; VCTE, vibration-controlled transient elastography

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changes during follow-up (e.g., meaningful weight loss, initiation of key cardiometabolic drugs, or differences in surveillance frequency) across strata would help readers interpret the findings in a real-world context; if such longitudinal data are not available, explicitly stating this would still be helpful for clinicians attempting to translate the results into practical algorithms.

In conclusion, Rabbat et al.[1] offer valuable multicenter data on a scenario that clinicians encounter daily, discordant FIB-4 and liver stiffness in MASLD. We hope that placing these findings alongside non-liver–related outcomes, time-specific absolute risks, and a brief description of follow-up care would help readers interpret discordant phenotypes in a broader clinical context and support more consistent pathway decisions.

Authors' contributions

Zhanna Zhang: conceptualization and manuscript draft.

Zichen Yu, Gongqiang Wu: critical revision for important intellectual content, final approval.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Rabbat J, Yang B, Lee HW, Lin H, Tsochatzis E, Petta S, et al. Histological severity and hepatic outcomes in patients with metabolic dysfunction-associated steatotic liver disease and discrepant FIB-4 and liver stiffness measurement. Clin Mol Hepatol 2026;32:289-304.
2. Stefan N, Yki-Järvinen H, Neuschwander-Tetri BA. Metabolic dysfunction-associated steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment. Lancet Diabetes Endocrinol 2025;13:134-148.
3. Issa G, Shang Y, Strandberg R, Hagström H, Wester A. Cause-specific mortality in 13,099 patients with metabolic dysfunction-associated steatotic liver disease in Sweden. J Hepatol 2025;83:643-651.
4. Chang M, Chang D, Kodali S, Harrison SA, Ghobrial M, Alkhouri N, et al. Degree of discordance between FIB-4 and transient elastography: an application of current guidelines on general population cohort. Clin Gastroenterol Hepatol 2024;22:1453-1461.e2.
5. Barbosa JV, Milligan S, Frick A, Broestl J, Younossi Z, Afdhal N, et al. Fibrosis-4 index can independently predict major adverse cardiovascular events in nonalcoholic fatty liver disease. Am J Gastroenterol 2022;117:453-461.
6. Yan Z, Liu Y, Li W, Zhao X, Lin W, Zhang J, et al. Liver fibrosis scores and prognosis in patients with cardiovascular diseases: a systematic review and meta-analysis. Eur J Clin Invest 2022;52:e13855.
7. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149:367-378.e5.
8. Rouillard NA, Barnett SD, Zhang X, Kam L, Manikat R, Cheung R, et al. Bariatric surgery reduces long-term mortality in patients with metabolic dysfunction-associated steatotic liver disease and cirrhosis. Clin Mol Hepatol 2025;31:227-239.
9. Singal AG, Zhang E, Narasimman M, Rich NE, Waljee AK, Hoshida Y, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: a meta-analysis. J Hepatol 2022;77:128-139.
10. Hernán MA, Wang W, Leaf DE. Target trial emulation: a framework for causal inference from observational data. JAMA 2022;328:2446-2447.