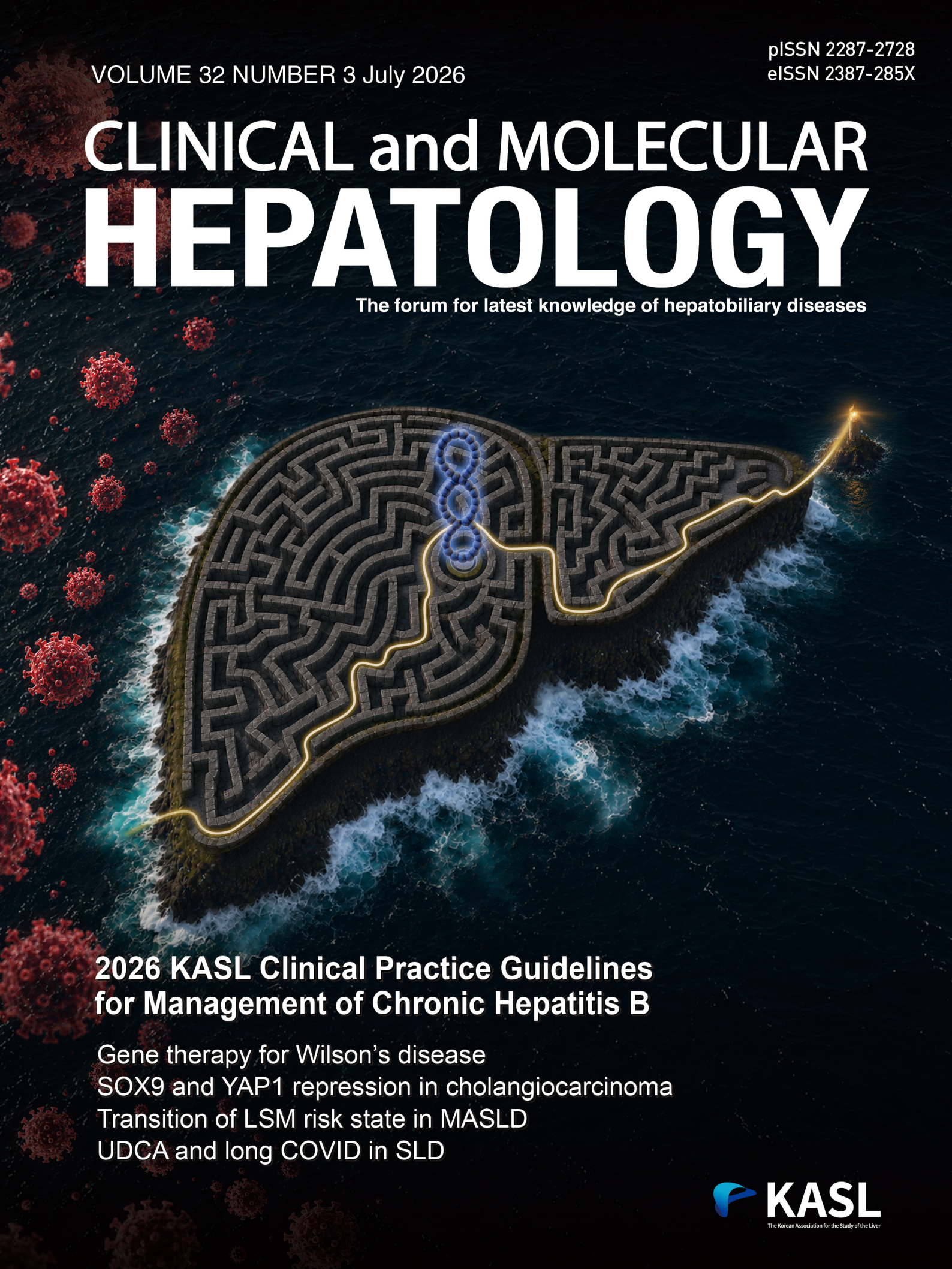


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Correspondence

Key challenges in cost-effectiveness analyses of emerging MASLD therapies: adherence, adverse events, cardiometabolic benefits, and age-related uncertainty: Correspondence to editorial on “Evaluating treatment response thresholds for cost-effective treatment in metabolic dysfunction-associated steatotic liver disease”

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Keywords: MASLD; Treatment; Cost-effectiveness; Fibrosis; Adherence

Dear Editor,

We sincerely appreciate the thoughtful editorial by Song et al. entitled “A cost-effectiveness evaluation framework for treatment for MASH: potential and concerns”, which provided an insightful and balanced discussion of our recent study evaluating cost-effectiveness thresholds for hy-

pothetical metabolic dysfunction-associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH) therapies.^{1,2} The authors highlighted both the strengths of our generalized modeling framework and several critical considerations—such as real-world adherence, metabolic comorbidities, and the heterogeneity of advanced fibrosis—that warrant careful interpretation. We

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fully acknowledge these points and would like to take this opportunity to clarify the interpretation of our findings in the context of economic evaluation principles.

The editorial rightly notes that real-world adherence is shaped by multiple factors, including adverse events and administration routes. These factors may substantially influence treatment persistence and, consequently, long-term cost-effectiveness beyond what can be reasonably assumed in model-based analyses.³ Our study revealed a seemingly paradoxical pattern in which higher adherence did not necessarily translate into a lower incremental cost-effectiveness ratio (ICER). This phenomenon is largely attributable to the fact that the simulations were anchored to the relatively high drug price, such that longer treatment persistence can increase cumulative costs more than the accrued benefits (extended life expectancy and QALYs). In our simulation, improved adherence extends life expectancy; however, the cumulative cost of the expensive drug over this extended survival period accrues faster than the health utility benefits, thereby keeping the ICER high.

The impact of adverse events on cost-effectiveness, especially those relating to dose, was not reflected in this analysis of a hypothetical agent. In contrast, GLP-1- and FGF21-class therapies have reported treatment-related adverse events and non-trivial discontinuation rates.^{4,5} Future economic evaluations should therefore incorporate dose-dependent adverse event profiles, discontinuation rates, and the associated management costs to refine cost-effectiveness estimates.

Regarding the impact of cardiovascular disease (CVD), our study showed a relatively modest effect of CVD reduction on the ICER. As detailed in Table 1A, the annual risk of severe cardiovascular (CV) events in our model ranges from 1.1% to 1.8% by the fibrosis stage from a previous study.⁶ Assuming the relative risk by treatment was 0.8 in our model, this translates to a net absolute risk reduction of 0.22–0.36%. In a hypothetical cohort of 10,000 patients (distributed as 50% F0–F2, 30% F3, and 20% F4), this corresponds to approximately 27 avoided CV events for one year (Table 1B). While a 20% relative risk reduction is clinically significant, the relatively low baseline absolute risk

limits the capacity of these avoided events to substantially drive overall cost-effectiveness through medical cost savings or QALY gains.

This result is partly because we modeled the cardiovascular benefit conservatively, focusing primarily on effects mediated through lipid lowering (e.g., LDL-C reduction). However, as the editorial suggests, emerging therapies such as GLP-1 receptor agonists may offer broader cardiometabolic benefits. Robust evidence regarding the long-term extrahepatic effects of emerging MASLD therapies remains limited, and comprehensively accounting for all extrahepatic pathways within a generalized economic model remains inherently challenging.^{7,8} Nevertheless, considering the significant impact of cardiometabolic risk factors on clinical outcomes, we agree that for future agents, the economic value attributable to preventing cardiovascular events will likely become a more dominant driver of cost-effectiveness alongside liver-related benefits.

The editorial also raised valid concerns about extrapolating results to older patients. We acknowledge the uncertainties regarding population variability. While the prevalence of advanced fibrosis (F3/F4), the incidence of malignancies including hepatocellular carcinoma (HCC), and the risk of CVD increase with age, our study did not fully capture these age-specific characteristics due to the lack of age-stratified efficacy data. To partially address this issue, we conducted sensitivity analyses using a cohort with a starting age of 60 years.¹ The estimated ICER falls slightly below the \$100,000/QALY threshold. This reflects the heightened clinical and economic uncertainty inherent in elderly populations, underscoring the need for future studies to evaluate cost-effectiveness specifically in distinct subgroups as real-world data accumulate.

In this study, treating only patients with F4 (cirrhosis) was the most cost-effective scenario, whereas treating only patients with F2 resulted in an ICER exceeding \$100,000/QALY, making it difficult to consider it cost-effective. However, this simulation can be interpreted as assuming a future agent with meaningful efficacy even in F4 disease. The magnitude of treatment effect in F4 may differ from that observed with agents such as semaglutide or resmeti-

Abbreviations:

CVD, cardiovascular disease; DC, decompensated cirrhosis; F2, fibrosis stage of 2; F3, fibrosis stage of 3; F4, fibrosis stage of 4; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; QALY, quality-adjusted life-years; WTP, willingness-to-pay

rom.^{9,10} Overall, these findings suggest that cost-effectiveness of MASLD therapies depends not only on an overall antifibrotic effect but also on fibrosis stage-specific regression, and that the degree of fibrosis improvement in F4 may be a key driver of the ICER.

In addition to the above description, we wish to address the editorial's comments regarding the high cost-effectiveness observed in the F4 (cirrhosis) group and the implications for F2 patients. Cost-effectiveness analysis is fundamentally a tool for assessing “efficiency”—specifically, “value for money.” It estimates the additional costs required to achieve one additional unit of health outcome. An intervention is deemed cost-effective if this value falls below the maximum willingness-to-pay (WTP) threshold of a society. A general principle in health economics is that interventions targeting more severe disease states often yield greater relative cost-effectiveness. This is because patients with severe disease (e.g., F4) face a high imminent risk of mortality and costly complications such as decompensation and HCC. Consequently, preventing progression in this high-risk group generates substantial “cost offsets” and significant survival or QALY gains compared to the lower-risk F2 group.

Importantly, this result (ICER exceeding WTP threshold) should not be misinterpreted as implying that the clinical value of treating F2 patients is low. While treating F2 patients may be “less efficient” in terms of ICER due to their lower baseline risk and longer time horizon to complications, preventing disease progression in early stages remains a critical clinical goal.

We thank Song et al. for their constructive comments. Our study was intended to provide a generalized framework to contextualize emerging MASLD trial data rather than to draw definitive conclusions about the value of specific therapies. We hope this clarification on the distinction between economic efficiency and clinical importance helps readers better interpret the value of MASLD treatments across different fibrosis stages.

Ethics approval statement

The study protocol was conducted in accordance with both the Declarations of Helsinki and was approved by the institutional review board of Hanyang University (IRB No. HY-2023-10-007). The requirement for informed consent was waived by the IRB due to the retrospective design of the study.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Study concept and design: All authors. Acquisition of data: Dae Won Jun and Hye-Lin Kim. Analysis and interpretation of data: All authors. Drafting of the manuscript: Jeong-Yeon Cho and Eileen L. Yoon. Critical revision and final approval of the manuscript: All authors. Statistical analysis: Jeong-Yeon Cho and Hye-Lin Kim. Study supervision: Dae Won Jun and Hye-Lin Kim.

Table 1. CVD risk in the analytic model

(A) CVD risk

Group stage	F0-F2	F3	F4	Total
Treatment	0.88%	1.11%	1.44%	-
No treatment	1.10% [*]	1.39% [*]	1.80% [*]	-
Difference	-0.22%	-0.28%	-0.36%	-

(B) Estimated number of CV events for one year

Group stage	F0-F2	F3	F4	Total
Hypothetical population, n	5,000	3,000	2,000	10,000
Treatment	44	33	29	106
No treatment	55	42	36	133
Difference	-11	-8	-7	-27

CVD, cardiovascular disease; CV, cardiovascular.

^{*}Ref. Loomba et al. (N Engl J Med 2023;389:998-1008).

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Conflicts of Interest

The authors have no conflicts to disclose.

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