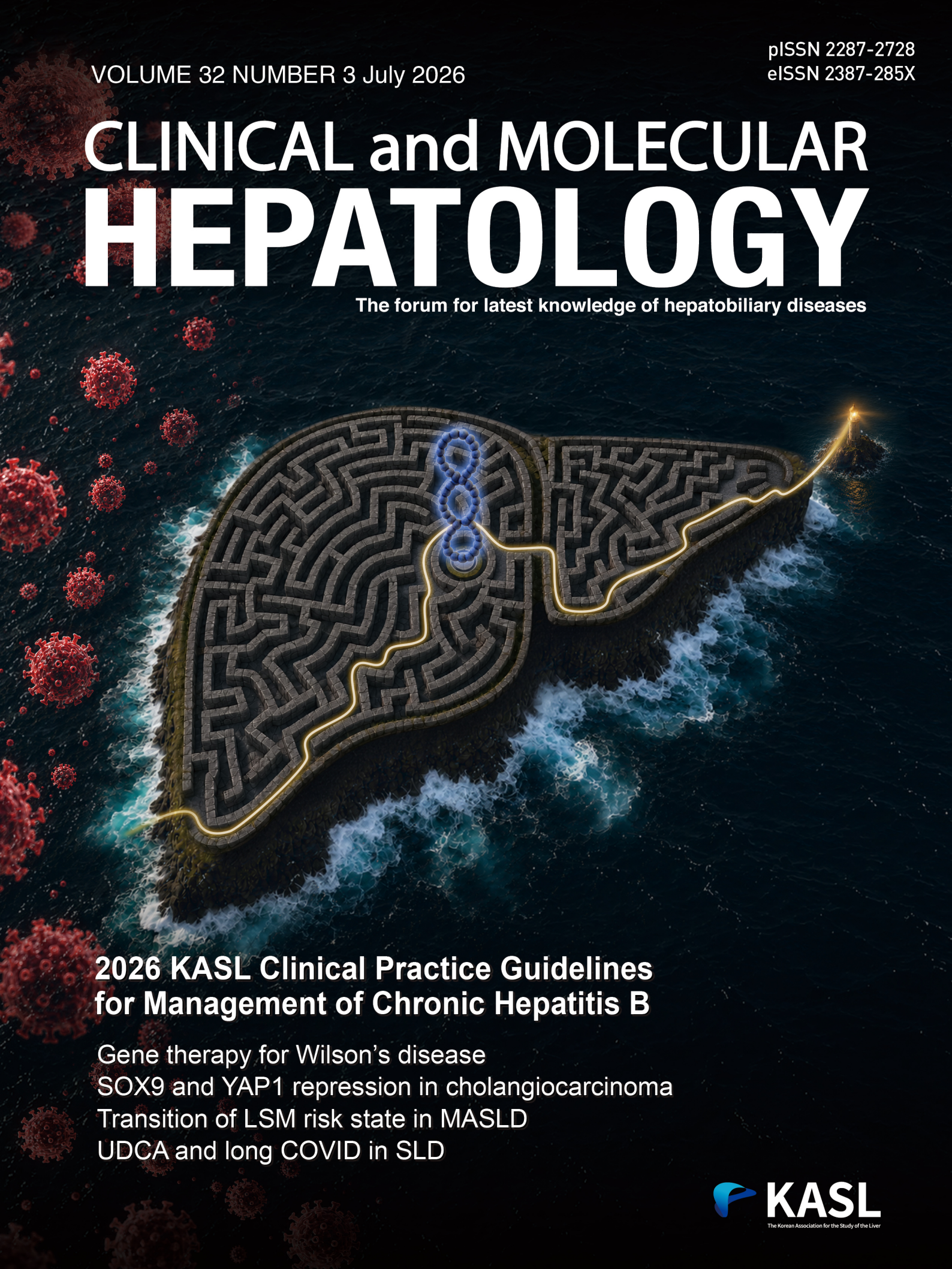


VOLUME 32 NUMBER 3 July 2026

pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases



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Incorporating chronic kidney disease into the cost-effectiveness of MASLD treatment: Correspondence to letter to the editor 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, chronic kidney disease

Dear Editor,

We sincerely thank Di Sessa et al. for their insightful letter to the editor regarding our recently published article.^{1,2} We appreciate their constructive comments highlighting the importance of chronic kidney disease (CKD) as a relevant systemic comorbidity in metabolic dysfunction-associated steatotic liver disease (MASLD) and important directions for future research.

As noted by the authors, numerous prospective cohort

studies have consistently reported a stepwise increase in the risk of incident CKD as the burden of liver fibrosis increases.³ For instance, in a cohort of patients with NAFLD, those with a higher NAFLD fibrosis score (NFS $\geq$ -1.455) had an approximately 1.58-fold higher risk of incident CKD compared to the non-NAFLD group.⁴ Furthermore, a study stratifying fibrosis stages using transient elastography in 5,983 patients with NAFLD found that advanced fibrosis (LSM $\geq$ 9.5 kPa) increased the risk of incident CKD by 5.40-fold compared to those without fibrosis (F0; <5.5 kPa).⁵

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Editor: Han Ah Lee, Chung-Ang University College of Medicine, Korea

Received: Jan. 20, 2026 / **Accepted:** Jan. 24, 2026

Similarly, in patients with type 2 diabetes and NAFLD, advanced fibrosis was associated with a significantly higher risk of incident CKD (adjusted hazard ratio ≈ 1.75), suggesting that liver fibrosis is a key risk stratification factor for renal prognosis.⁶ Given that CKD also substantially impacts health-related quality of life (HRQoL),^{7,8} incorporating CKD into economic evaluations is likely to further enhance the cost-effectiveness of the hypothetical therapy.

Although our original model did not explicitly include a CKD state to maintain model simplicity, we acknowledge that this exclusion likely led to a conservative estimation of the hypothetical drug's cost-effectiveness. To illustrate this point, we performed a supplementary estimation applying the fibrosis stage-specific incidence rates of CKD to our Markov model over 10 years (Table 1). In this supplementary simulation, we estimated the potential reduction in CKD incidence based solely on the indirect protective effects mediated by liver fibrosis regression. To maintain model parsimony while ensuring a conservative estimate, we applied the following specific assumptions:

- Number of individuals in the hypothetical cohort: 10000 (fibrosis stage distribution, F2:F3 = 40%:60%)

- Treatment effect assumption for fibrosis stage improvement (response gap between hypothetical drug X and no treatment): same as our original study
 - initial response rate gap: 25%
 - minimal sustained durability gap: 2%
- CKD risk by fibrosis stage⁹
 - rate per 100 person-yr: 2.17 in F0-F2, 2.97 in F3, 4.49 in F4
 - Health utility index decrement by CKD⁸: -0.18
- Assumptions regarding CKD state and the treatment effect on kidney function
 - Homogeneity of CKD state: Incident CKD was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² without stratifying between CKD stages 3, 4, and 5.
 - Efficacy: We applied a conservative assumption that hypothetical drug has no direct renoprotective effect, attributing all renal risk reduction strictly to the improvement in liver histology.

As shown in the simulation, the Drug X-treatment group, which achieved fibrosis regression, had a lower cumulative incidence of CKD events (2,333 vs. 2,615) and less total

Table 1. Simulation of CKD incidence and associated QALY loss based on fibrosis regression by a hypothetical MASLD treatment

Cycle (year)	Treatment						No treatment					
	F0-F1	F2	F3	F4	CKD	QALY loss by CKD	F0-F1	F2	F3	F4	CKD	QALY loss by CKD
0	–	4,000	6,000	–	–	–	0	4,000	6,000	0	–	–
1	1,313	4,647	3,998	0	265	47.7	315	3,688	5,411	545	265	47.7
2	2,117	4,641	3,156	0	248	44.7	572	3,420	4,881	966	272	49.0
3	2,540	4,621	2,702	0	240	43.3	781	3,184	4,407	1,283	275	49.5
4	2,810	4,595	2,401	0	236	42.4	951	2,973	3,986	1,514	275	49.4
5	3,035	4,545	2,162	0	232	41.8	1,091	2,781	3,611	1,674	272	48.9
6	3,258	4,469	1,947	0	229	41.2	1,205	2,605	3,280	1,777	266	48.0
7	3,469	4,378	1,754	0	226	40.6	1,298	2,442	2,985	1,834	260	46.8
8	3,665	4,275	1,581	0	222	40.0	1,373	2,289	2,722	1,855	252	45.4
9	3,844	4,164	1,427	0	219	39.5	1,433	2,146	2,487	1,846	244	43.8
10	4,007	4,048	1,289	0	216	38.9	1,481	2,011	2,276	1,816	234	42.2
Cumulative					2,333	420					2,615	471

CKD, chronic kidney disease; MASLD, metabolic dysfunction-associated steatotic liver disease; QALY, quality-adjusted life-year.

Abbreviations:

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; F2, fibrosis stage of 2; F3, fibrosis stage of 3; F4, fibrosis stage of 4; ICER, incremental cost-effectiveness ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; QALY, quality-adjusted life-years

QALY loss related to CKD (420.0 vs. 470.6) compared to those of non-treatment group over the 10-year horizon. This demonstrates that if the renal benefits of fibrosis regression were accounted for, the hypothetical drug would generate even greater health utility gains and potential cost savings from avoided kidney disease.

However, most cost-effectiveness analyses of MASLD therapeutics, including our own, have not fully incorporated or rigorously evaluated the benefits regarding the prevention or delayed progression of CKD to date. Therefore, we consider the suggestion to integrate CKD into economic evaluations to be valid and highly significant from both clinical and policy perspectives. To accurately model the costs and health effects associated with CKD in future economic evaluations of MASLD therapies, several key lines of evidence must first be established:

First, robust evidence is needed to quantify the magnitude of the impact of liver fibrosis regression on changes in renal function (e.g., eGFR) and the risk of incident CKD. While studies reporting an association between MASLD fibrosis severity and CKD are relatively abundant,³ long-term prospective data quantifying the effect size—specifically, how much MASLD progression or regression drives renal deterioration or recovery—remain insufficient. Furthermore, data are required to determine whether novel therapeutic agents possess “direct renoprotective effects” beyond the indirect benefits mediated by fibrosis improvement, and to what extent these effects translate into reduced CKD incidence or delayed progression. Second, evidence regarding the secondary mediation effect of renal function changes—resulting from MASLD progression or treatment—on major adverse cardiovascular events is essential. As prospective clinical evidence accumulates, particularly for agents with reported cardiorenal benefits such as GLP-1 receptor agonists, we anticipate that “holistic” economic evaluations integrating liver improvement, cardiovascular risk reduction, and renal protection will become feasible. Third, quantitative evidence regarding the effect of currently approved or investigational therapies (e.g., resmetirom, GLP-1 receptor agonists) on renal function improvement is still limited. Consequently, there is substantial uncertainty in accurately estimating how renal functional improvements driven by MASLD treatment translate into QALY gains and ICER improvements.

In conclusion, the ICER derived in our study should be inter-

preted as a conservative “upper bound” for the cost-effectiveness ratio. Given that CKD is associated with substantial healthcare costs and marked deterioration in health-related quality of life, the actual economic value of MASLD treatment may be greater than that suggested by our model, particularly if renal benefits are present, either directly or indirectly. We strongly concur with the perspective of Di Sessa et al. that future economic evaluations must evolve into ‘multi-organ disease models’. Such comprehensive frameworks, capturing not only liver-related outcomes but also cardiovascular and renal benefits, are essential for informing more holistic and accurate clinical decision-making.

Ethics approval statement

The study protocol was conducted in accordance with both the Declarations of Helsinki and Istanbul 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’ contribution

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.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2023-00217123), and Research Program funded by the Korea National Institute of Health (grant number: 2025-ER0902-01).

Conflicts of Interest

The authors have no conflicts to disclose.

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