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Letter to the Editor

Letter to the Editor: Genotype-specific Response to 144-week Entecavir Therapy for HBeAg-positive Chronic Hepatitis B with a Particular Focus on Histological Improvement: A Prospective Study

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Dear Editors,

We read with great interest the prospective study by Liu et al. in the Journal of Clinical and Translational Hepatology.[1] Using paired liver biopsies, the authors reported superior histological improvement with 144-week entecavir therapy in HBeAg-positive chronic hepatitis B (CHB) patients with HBV genotype B versus genotype C.[1] While this work fills a key evidence gap on genotype-specific intrahepatic benefits of long-term nucleos(t)ide analogues and informs personalized CHB management, we raise two substantive concerns regarding its study design and result interpretation that may undermine the robustness of the core conclusions.

First, the primary histological endpoint is inconsistently defined between the abstract and methods section. The abstract defines the primary endpoint as "≥2-grade reduction in necroinflammatory activity without fibrosis progression".[1] By contrast, the methods section explicitly defines that the primary efficacy endpoint was the overall histological response, which included both a ≥1-grade reduction (effective response) and a ≥2-grade reduction (very effective response) in necroinflammatory activity.[1]

The predefined primary endpoint is the cornerstone of clinical trial result interpretation, and inconsistent endpoint definitions may lead to selective reporting bias, in accordance with the core principles of the CONSORT statement.[2] As histological improvement is a validated core surrogate endpoint for cirrhosis and hepatocellular carcinoma risk reduction in CHB, this inconsistency may overestimate the genotype-specific treatment effect and mislead clinical decision-making. Notably, the reported $P = 0.027$ corresponds to the pre-specified primary endpoint (≥1-grade reduction), while the very effective response (≥2-grade reduction) rates were 78.3% for genotype B vs. 21.1% for genotype C (original study Table 2), with no between-group *P*-value reported (we calculated $P < 0.001$ via Fisher's exact test, Table 1 of this letter).[1] This inconsistency should be clarified to confirm the reliability of the core findings.

Second, the study overinterprets the causal link between HBV genotype and histological improvement without sufficient mechanistic support, and its clinical recommendation is misaligned with the study's design and applicable population. The authors showed that baseline HBV DNA (7.8 vs. 7.3 $\log_{10}$ IU/mL, $P = 0.003$) and HBeAg levels (934.3 vs. 439.7 S/CO, $P = 0.007$) were significantly higher in genotype B patients than in genotype C patients.[1] Meanwhile, both genotypes achieved 100% virological suppression at week 96, and genotype C had a numerically higher HBeAg seroconversion rate (50.0% vs. 29.2%, $P = 0.140$, no statistically significant difference).[1]

However, the authors attributed the superior histological improvement to HBV genotype itself, without multivariable adjustment to exclude confounding from baseline viral imbalances. We request the authors to provide adjusted analyses to clarify the independent effect of HBV genotype on histological improvement and to explain the persistent difference in intrahepatic inflammation resolution despite universal virological suppression. Notably, the study did not assess key virological markers, including intrahepatic HBcAg and serum/intrahepatic HBsAg, which may partially explain the observed histological discrepancy.

Additionally, genotype comparisons were limited to 42 patients (23 genotype B, 19 genotype C) from a single center, exclusively enrolling HBeAg-positive non-cirrhotic Chinese patients. This small sample size increases statistical variability and type I error (false-positive) risk, further amplified by unadjusted multiple subgroup and endpoint analyses. While we acknowledge the study notes its small sample and single-center limitations, its recommendation to incorporate HBV genotyping into routine clinical practice remains overly broad and unsupported by its narrow study population. This aligns with the latest EASL, AASLD, and APASL CHB guidelines,[3–5] which all call for validation in large-scale, multicenter, diverse cohorts before such broad implementation in routine clinical practice.

To confirm the robustness of the study's conclusions, we

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Table 1. Comparison of histological response rates between HBV genotype B and C according to the pre-specified primary endpoint and the abstract-reported endpoint in the original studyby Liu *et al*.[1]

Definition of histological response endpoint	Genotype B (n = 23)	Genotype C (n = 19)	*P*-value
Pre-specified primary endpoint in the Methods section (≥1-grade reduction in necroinflammatory activity without fibrosis progression)	21 (91.3%)	12 (63.2%)	0.027 (reported in original article)
Reported endpoint in the Abstract section (≥2-grade reduction in necroinflammatory activity without fibrosis progression)	18 (78.3%)	4 (21.1%)	<0.001*

*Note: This *P*-value was calculated using Fisher's exact test based on the raw data from the original article; the between-group *P*-value for this endpoint was not separately reported in the original article.

propose the following concrete suggestions for the authors: (1) Reconfirm the pre-specified primary endpoint and reanalyze data using a consistent definition aligned with CONSORT principles; (2) Perform multivariable regression adjusting for baseline confounders (HBV DNA, HBeAg levels) to clarify the independent effect of HBV genotype on histological improvement; (3) Refine clinical conclusions and recommendations to fully reflect the study's limitations (small sample size, single-center design, narrow population, insufficient mechanistic exploration); (4) Report the between-group *P*-value for the ≥2-grade reduction endpoint via appropriate tests (e.g., Fisher's exact test), and clarify whether multiple comparison adjustments were applied to all secondary and subgroup analyses.

Overall, this study provides valuable prospective paired liver biopsy data on genotype-specific histological responses to long-term entecavir therapy. We hope the authors will address the above concerns to further verify the robustness of their conclusions. We thank the authors for their contribution to the field and look forward to their response.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Witing-original draft preparation (CY), writing-review and editing (LW). All authors have approved the final version and publication of the manuscript.

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