



Research Letter



qHBsAg Trajectories with Peg-IFN α -2b Add-on Therapy in Nucleos(t)ide Analog-experienced HBeAg-positive Chronic Hepatitis B

Kezhen Hu^{1,2#}, Yanzhen Bi^{2#}, Xiaoying Li³, Xiangzhong Liu⁴, Haoxi Wang⁵, Yong Zhou^{6*} and Yongning Xin^{2*}

¹Qingdao Municipal Hospital, Qingdao University, Qingdao, Shandong, China; ²Department of Infectious Diseases, Qingdao Municipal Hospital, Qingdao, Shandong, China; ³Shandong Public Health Clinical Center, Shandong University, Jinan, Shandong, China; ⁴Department of Liver Diseases I, Yantai Qishan Hospital, Yantai, Shandong, China; ⁵University of Science and Technology of China, Hefei, Anhui, China; ⁶Department of Liver Diseases II, Qingdao Sixth People's Hospital, Qingdao, Shandong, China

Received: March 09, 2026 | Revised: June 10, 2026 | Accepted: June 24, 2026 | Published online: July 24, 2026

Citation of this article: Hu K, Bi Y, Li X, Liu X, Wang H, Zhou Y, et al. qHBsAg Trajectories with Peg-IFN α -2b Add-on Therapy in Nucleos(t)ide Analog-experienced HBeAg-positive Chronic Hepatitis B. *J Clin Transl Hepatol* 2026;14(8):879–882. doi: 10.14218/JCTH.2026.00175.

HBsAg loss is a preferred virological endpoint for functional cure in chronic hepatitis B (CHB),¹ yet it remains uncommon within finite treatment durations, particularly under long-term nucleos(t)ide analogs (NAs) therapy.^{2,3} Pegylated interferon alpha-2b (Peg-IFN α -2b) may increase the probability of HBsAg decline and loss in selected patients; however, in small real-world cohorts, the limited number of HBsAg loss events often leads to imprecise estimates and uncertainty. Moreover, a binary endpoint (HBsAg loss vs. non-loss) does not capture on-treatment qHBsAg dynamics, which are measured irregularly in routine practice.^{4,5} To better characterize on-treatment qHBsAg dynamics in real-world settings with irregular sampling and sparse endpoint events, we visualized qHBsAg trajectories using locally estimated scatterplot smoothing (LOESS) in NA-experienced patients who initiated Peg-IFN α -2b add-on therapy while continuing NAs and in those who continued NAs alone. Accordingly, the primary aim was to compare on-treatment qHBsAg trajectories between the two groups, and the secondary aim was to compare HBsAg loss within 500 days, thereby potentially informing treatment selection and monitoring strategies for this subgroup of patients with CHB.

We conducted a real-world, multicenter, prospective cohort study from February 2023 to October 2025 at several sites in Shandong Province, evaluating Peg-IFN α -2b add-on therapy in NA-experienced, HBeAg-positive patients with

CHB who had received continuous NA therapy for at least 12 months before baseline and had baseline HBsAg <3,000 IU/mL. To compare HBsAg dynamics between the Peg-IFN α -2b add-on group and the NAs-alone group, we extracted electronic health record data from hospital information systems and formed a concurrent control cohort of patients who received NAs alone. Missing data were handled using an available-case approach without imputation. Details regarding missing data handling, qHBsAg measurement frequency per patient, and Peg-IFN α -2b discontinuation criteria are provided in Supplementary Appendix 1. Baseline (Day 0) was defined as the date of the first Peg-IFN α -2b prescription for the Peg-IFN α -2b add-on group and, for the NAs-alone group, the first eligible clinic visit between 2023 and 2025 at which qHBsAg was measured and all inclusion criteria were met. Continuous NA therapy for ≥ 12 months prior to baseline was verified using prescription records documented in the electronic medical record. The date when NAs were continued was defined as the most recent NA prescription date prior to baseline, which was used to confirm that patients remained under NA treatment coverage at baseline. Time for each qHBsAg measurement was expressed in days relative to baseline. We excluded coinfection with HCV/HDV/HIV, other chronic liver diseases (alcohol-related, drug-induced, autoimmune), moderate-to-severe nonalcoholic steatohepatitis, hepatocellular carcinoma, and telbivudine use. Data were primarily extracted from electronic health records; paper-based laboratory reports were digitized and structured using MedSyntix. In total, 161 patients received Peg-IFN α -2b add-on therapy while continuing NAs and 205 patients continued NAs alone, from whom all available pre-baseline and post-baseline measurements of qHBsAg, qHBeAg, white blood cell (WBC) counts, and platelet (PLT) counts were collected.

We performed one-to-one nearest-neighbor propensity score matching (PSM) without replacement using the logit-transformed propensity score. The propensity score was estimated using a logistic regression model including age, sex, WBC count, neutrophil count, hemoglobin, PLT count, and qHBsAg. All included patients had received continuous NA therapy for at least 12 months before baseline, and baseline hepatitis B virus (HBV) DNA was <500 IU/mL in the included

#Contributed equally to this work.

*Correspondence to: Yongning Xin, Department of Infectious Diseases, Qingdao Municipal Hospital, Qingdao, Shandong 266011, China. ORCID: <https://orcid.org/0000-0002-3692-7655>. Tel: +86-532-82789463, Fax: +86-532-85968434, E-mail: xinyongning@163.com; Yong Zhou, Department of Liver Diseases II, Qingdao Sixth People's Hospital, Qingdao, Shandong 266011, China. ORCID: <https://orcid.org/0000-0003-4615-5879>. Tel: +86-15588994752, Fax: +86-532-88905831, E-mail: zhouyong197902@163.com.

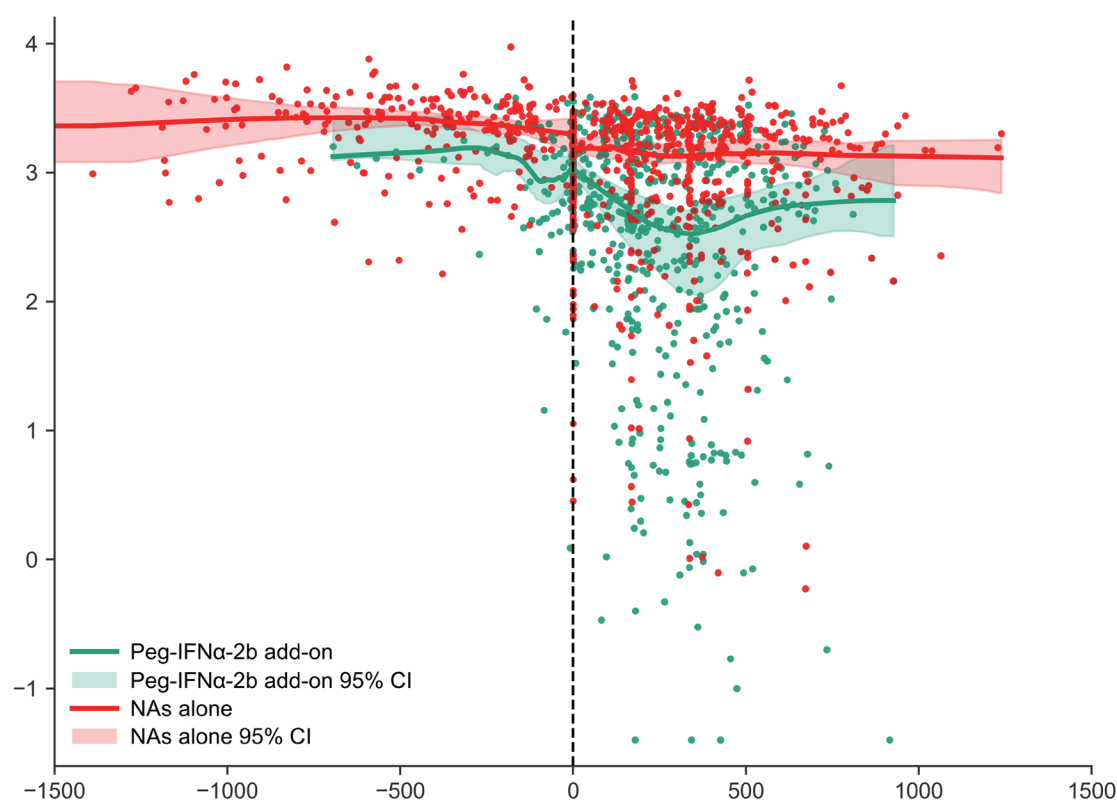


Fig. 1. LOESS-smoothed trajectories of qHBsAg under Peg-IFN α -2b add-on versus NAs alone. Points are individual qHBsAg measurements (green denotes Peg-IFN α -2b add-on, and red represents NAs alone); solid lines denote the LOESS fit, and shaded ribbons show 95% CIs. The vertical dashed line marks baseline. The x-axis shows time (days) relative to baseline; negative values indicate pre-baseline measurements. The y-axis shows qHBsAg (log₁₀ IU/mL). Number of qHBsAg measurements: Peg-IFN α -2b add-on group, $n = 563$; NAs-alone group, $n = 604$. Pre-baseline trajectories represent available historical qHBsAg measurements and are intended only to provide descriptive context. NAs, nucleos(t)ide analogs; Peg-IFN α -2b, pegylated interferon alpha-2b; LOESS, locally estimated scatterplot smoothing; CI, confidence interval.

cohort; therefore, HBV DNA showed limited variability and was not included in the primary propensity score model. Matching was conducted with a caliper width of 0.2 standard deviations of the logit of the propensity score. Given irregular real-world sampling and a priori unknown trajectory shape, we visualized qHBsAg dynamics using piecewise LOESS (span = 0.50) fitted separately before and after baseline within each group. LOESS does not require prespecifying a global functional form or knot structure and leverages all available observations on a continuous time scale to depict key dynamic features of qHBsAg. To contextualize the qHBsAg dynamics with a functional cure endpoint, the Kaplan-Meier method was used to estimate cumulative incidence of HBsAg loss (≤ 0.05 IU/mL), with administrative censoring at day 500. Methodological details for missing data handling, PSM, LOESS, Kaplan-Meier analyses, and WBC/PLT/qHBsAg trajectories are provided in Supplementary Appendixes 1–6. All analyses were performed in R version 4.4.1 (MatchIt, survival, survminer, and ggplot2).

After PSM, 161 matched pairs were formed, and baseline covariates were well balanced. Peg-IFN α -2b add-on therapy was generally planned as a finite-duration course of approximately 48 weeks when clinically feasible. The median actual treatment duration was 315 days (interquartile range, 172–350). In the Peg-IFN α -2b add-on group, 27/161 patients (16.8%) received Peg-IFN α -2b for <24 weeks, 95/161 (59.0%) for 24–48 weeks, and 39/161 (24.2%) for >48 weeks. Overall, 64/161 patients (39.8%) received Peg-IFN α -2b for at least 48 weeks.

All qHBsAg measurements for each patient were includ-

ed, including both pre-baseline and post-baseline tests. The Peg-IFN α -2b add-on group contributed 563 qHBsAg visits, and the NAs-alone group contributed 604 qHBsAg visits. We characterized qHBsAg trajectories and observed markedly different patterns between the Peg-IFN α -2b add-on group and the NAs-alone group (Fig. 1).

In the Peg-IFN α -2b add-on group, qHBsAg declined rapidly after Peg-IFN α -2b initiation. Fitted curves reached the nadir around 10–12 months, followed by a modest rebound. The nadir value was 2.48 (95% confidence interval [CI], 2.38–2.61) log₁₀ IU/mL. In contrast, the NAs-alone group showed a minimal decline over time, with no apparent change in trajectory across baseline. By month 10, 81/161 patients (50.3%) had discontinued Peg-IFN α -2b, suggesting that the modest qHBsAg rebound at approximately 10–12 months may have temporally coincided with treatment discontinuation.

The number of individuals at risk decreased substantially after day 500; the tail of the Kaplan-Meier curves became unstable, and the 95% CIs widened markedly. Therefore, an administrative truncation at day 500 was applied in the time-to-event analyses to minimize the impact of sparse data. Within 500 days, three patients in the Peg-IFN α -2b add-on group achieved HBsAg ≤ 0.05 IU/mL, whereas none in the NAs-alone group did. The Kaplan-Meier curves did not differ significantly between groups, although a trend toward higher cumulative HBsAg loss was observed in the Peg-IFN α -2b add-on group (log-rank $P = 0.06$; Fig. 2).

In this study, Peg-IFN α -2b therapy was associated with an early decline in qHBsAg followed by a modest rebound,

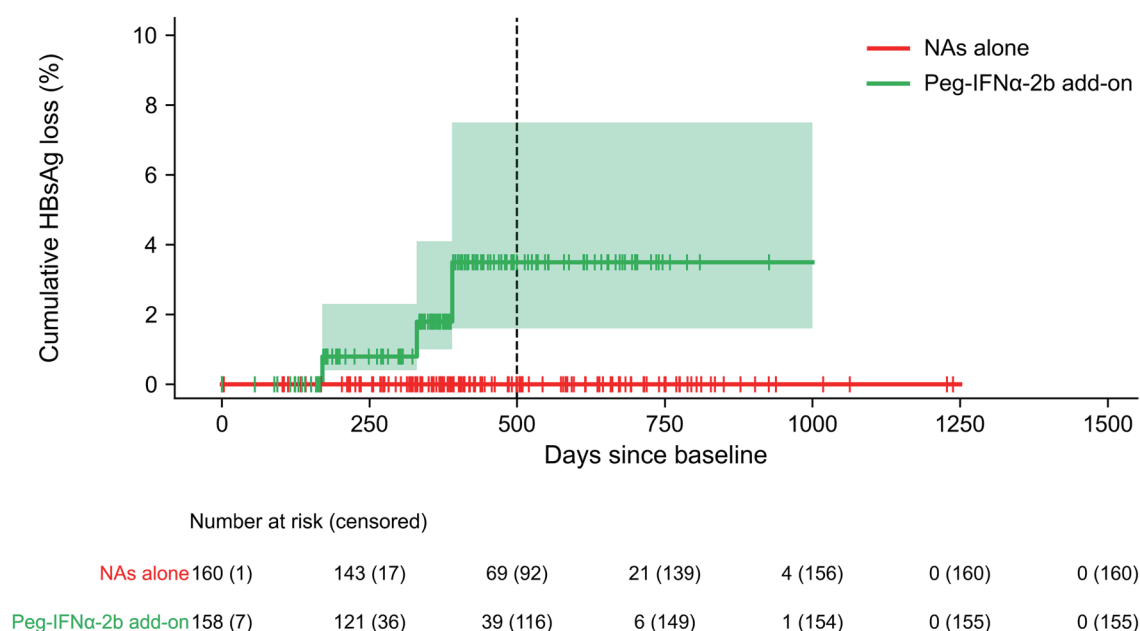


Fig. 2. Kaplan-Meier curves of HBsAg loss (Peg-IFN α -2b add-on vs. NAs alone). Green denotes Peg-IFN α -2b add-on, and red denotes NAs alone. Shaded areas indicate 95% CIs. The vertical dotted line indicates the administrative truncation point at day 500. The x-axis is displayed up to 1,500 days for visualization; however, statistical comparisons were administratively truncated at day 500, and data beyond day 500 are presented descriptively without inferential comparison. Numbers at risk are shown below the plot. The number outside the parentheses represents the number of patients at risk, while the number inside the parentheses represents the cumulative number of censored patients. The cross marks indicate censoring points. NAs, nucleos(t)ide analogs; Peg-IFN α -2b, pegylated interferon alpha-2b; CI, confidence interval.

whereas the NAs-alone cohort showed little change over time. LOESS suggested this pattern, despite the modest sample size, may help inform clinicians' treatment decisions and follow-up planning for these patients. A partial rebound in qHBsAg after discontinuation of Peg-IFN α -2b has been previously noted,⁶ although it has seldom been presented as a continuous trajectory. Because only three participants reached the binary endpoint of HBsAg ≤ 0.05 IU/mL, the Kaplan-Meier analysis primarily summarizes time to HBsAg loss, while LOESS-based trajectories complement it by providing a more intuitive view of continuous post-treatment qHBsAg dynamics. Exploratory WBC, PLT, and qHBeAg trajectories are shown in Supplementary Appendix 5. WBC and PLT declined early after Peg-IFN α -2b initiation and then gradually recovered, consistent with the expected effects of Peg-IFN α -2b exposure. The qHBeAg trajectory suggested a more rapid early decline in the Peg-IFN α -2b add-on group during the first six months after baseline, although subsequent rates of decline became broadly comparable between groups. As functional cure regimens are increasingly evaluated in studies with sparse endpoint events, trajectory-based visualization may complement endpoint-driven analyses by capturing clinically meaningful on-treatment qHBsAg dynamic features. The small number of HBsAg loss events limited statistical power and clinical interpretation of this endpoint; therefore, HBsAg loss should be interpreted cautiously. Alanine aminotransferase (ALT) normalization could not be reliably evaluated because ALT data were incomplete and were not consistently available at the prespecified time points, which represents an additional limitation of this real-world analysis.

Peg-IFN α , as a finite-duration immunomodulatory therapy, is generally associated with modest qHBsAg reductions, whereas sustained off-treatment responses occur only in a proportion of patients.⁷ Mechanistically, Peg-IFN α has been shown to repress the HBV cccDNA minichromosome via

HDAC3-associated histone modifications, thereby suppressing cccDNA-driven transcription and contributing to qHBsAg decline.⁸ In parallel, immunologic mechanisms may reinforce this on-treatment decrease. Peg-IFN α has been reported to enhance natural killer cell-mediated inhibition of regulatory T cells, which is associated with greater qHBsAg decline.⁹ Moreover, in HBeAg-positive CHB patients receiving Peg-IFN α , those achieving HBeAg seroconversion exhibited higher levels of C-X-C chemokine receptor type 5 (CXCR5)⁺CD8⁺ T cells with a sustained increase during therapy, and CXCR5 expression on CD8⁺ T cells was inversely correlated with HBsAg levels.¹⁰ The modest HBsAg rebound observed after Peg-IFN α -2b discontinuation may reflect attenuation of interferon-induced transcriptional repression, allowing partial restoration of low-level transcriptional output from residual intrahepatic cccDNA reservoirs.¹¹ Notably, precore and basal core promoter variants have been linked to higher post-withdrawal relapse risk in HBeAg-positive CHB, although evidence largely comes from NA discontinuation cohorts, raising the possibility that persistent variant reservoirs could also modulate post-Peg-IFN α qHBsAg dynamics.¹² Compared with NA monotherapy, interferon-based therapy has been associated with a lower long-term risk of incident cirrhosis in real-world cohort studies.¹³

Several limitations should be acknowledged though. First, although PSM improved baseline comparability, this study remained a real-world observational study with a concurrent but non-randomized control cohort and therefore cannot establish causal relationships. Residual confounding by indication or unmeasured factors, such as treatment adherence and prior response to NAs, cannot be excluded. Second, PSM can only account for measured variables included in the model. Although background NA regimens were summarized in the Supplementary Materials, baseline ALT data, duration of prior NA therapy, treatment-switching history, treatment

adherence, additional markers of liver disease severity, and HBV genotype were incompletely recorded or not routinely tested, which may have contributed to residual confounding. Detailed reasons for Peg-IFN α -2b discontinuation were also not consistently documented, limiting further analysis of treatment discontinuation patterns. In addition, variable Peg-IFN α -2b treatment duration may have influenced the qHBsAg trajectory shape. Third, the study population was highly selected, including only NA-experienced, HBeAg-positive CHB patients with baseline HBsAg <3,000 IU/mL. Therefore, our findings should not be extrapolated to treatment-naïve patients, HBeAg-negative patients, patients with higher baseline HBsAg levels, or other CHB populations. Future prospective studies with more complete clinical and virological data are needed to validate our findings in broader CHB populations.

In summary, among NA-experienced, HBeAg-positive patients with CHB and baseline HBsAg <3,000 IU/mL, Peg-IFN α -2b add-on therapy was associated with a rapid early decline in qHBsAg followed by a modest rebound, whereas continued NAs alone showed minimal change. Although the between-group difference in HBsAg loss did not reach statistical significance, a trend toward higher cumulative HBsAg loss was observed in the Peg-IFN α -2b add-on group. LOESS trajectories offer an intuitive way to visualize qHBsAg dynamics in small real-world cohorts with irregular sampling and few HBsAg loss events, with potential implications for treatment and monitoring planning in this subgroup of patients with CHB.

Supporting information

Supplementary material for this article is available at <https://doi.org/10.14218/JCTH.2026.00175>.

Acknowledgments

We thank MedSyntix for extracting data from paper-based laboratory reports and converting them into structured digital tables.

Funding

This research was funded by the National Natural Science Foundation of China (32171277, 82202416), the China Hepatitis Prevention and Control Foundation Mu Xin Chronic Hepatitis B Research Fund (MX202409), the Beijing iGandan Foundation Clinical Research Project (iGandanF-1082024-LG002), the Qingdao Medical and Health Research Guidance Project (2023-WJZD173), and the Qingdao Key Medical and Health Discipline Project.

Conflict of interest

YX has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Formal statistical analysis, drafting of the original manuscript

(KH), data collection, data curation (XyL, XzL), guidance on data analysis, preparation of figures (HW), study conceptualization, and critical revision of the manuscript (YZ, YB, YX). All authors read, revised, and approved the final manuscript.

Ethical statement

The study was approved by the Ethics Committee of Qingdao Municipal Hospital (No. 2023 LSZD-Y004) and conducted in accordance with the Declaration of Helsinki (as revised in 2024). Written informed consent was obtained from all participants prior to enrollment, and the study was registered in the Chinese Clinical Trial Registry (ChiCTR2500108331).

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

- [1] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2025;83(2):502–583. doi:10.1016/j.jhep.2025.03.018, PMID:40348683.
- [2] Wang Z, Wang X, Zhou L, Shi S, Hua Y, Feng Y. Safety and efficacy of 48-week pegylated interferon- α -2b therapy in patients with hepatitis B virus-related compensated liver cirrhosis: a pilot observational study. *Front Med (Lausanne)* 2024;11:1489671. doi:10.3389/fmed.2024.1489671, PMID:39697201.
- [3] You H, Wang F, Li T, Xu X, Sun Y, Nan Y, *et al*. Guidelines for the Prevention and Treatment of Chronic Hepatitis B (version 2022). *J Clin Transl Hepatol* 2023;11(6):1425–1442. doi:10.14218/JCTH.2023.00320, PMID:37719965.
- [4] Liaw YF, Papatheodoridis G. Finite nucleos(t)ide analog therapy for functional cure in HBeAg-negative chronic hepatitis B: Recent development in the paradigm shift. *Hepatology* 2026;83(3):679–692. doi:10.1097/HEP.0000000000001107, PMID:39316697.
- [5] Hsu WF, Chen CF, Lai HC, Su WP, Wang HW, Chen SH, *et al*. Trajectories and Decline of Serum Hepatitis B Surface Antigen Predict Outcomes in Patients With Chronic Hepatitis B. *Open Forum Infect Dis* 2024;11(12):ofae699. doi:10.1093/ofid/ofae699, PMID:39679354.
- [6] Sun J, Ma H, Xie Q, Xie Y, Sun Y, Wang H, *et al*. Response-guided peginterferon therapy in patients with HBeAg-positive chronic hepatitis B: A randomized controlled study. *J Hepatol* 2016;65(4):674–682. doi:10.1016/j.jhep.2016.05.024, PMID:27238752.
- [7] Wu D, Kao JH, Piratvisuth T, Wang X, Kennedy PTF, Otsuka M, *et al*. Update on the treatment navigation for functional cure of chronic hepatitis B: Expert consensus 2.0. *Clin Mol Hepatol* 2025;31(Suppl):S134–S164. doi:10.3350/cmh.2024.0780, PMID:39838828.
- [8] Zhao LN, Yuan HF, Wang YF, Yun HL, Zheng W, Yuan Y, *et al*. IFN- α inhibits HBV transcription and replication by promoting HDAC3-mediated de-2-hydroxyisobutyrylation of histone H4K8 on HBV cccDNA minichromosome in liver. *Acta Pharmacol Sin* 2022;43(6):1484–1494. doi:10.1038/s41401-021-00765-7, PMID:34497374.
- [9] Yuan W, Huang D, Wu D, Chen Y, Ma K, Han M, *et al*. Pegylated Interferon- α (IFN- α) Enhances the Inhibitory Effect of Natural Killer Cells on Regulatory T Cells via IFN- γ in Chronic Hepatitis B. *J Infect Dis* 2021;224(11):1878–1889. doi:10.1093/infdis/jiab216, PMID:33870432.
- [10] Xu ZY, Dai ZS, Gong GZ, Zhang M. C-X-C chemokine receptor type 5(+) CD8(+) T cells as immune regulators in hepatitis Be antigen-positive chronic hepatitis B under interferon-alpha treatment. *World J Gastroenterol* 2025;31(3):99833. doi:10.3748/wjg.v31.i3.99833, PMID:39839901.
- [11] Ren J, Cheng S, Ren F, Gu H, Wu D, Yao X, *et al*. Epigenetic regulation and its therapeutic potential in hepatitis B virus covalently closed circular DNA. *Genes Dis* 2025;12(1):101215. doi:10.1016/j.gendis.2024.101215, PMID:39534573.
- [12] Xia S, He X, Gan J, Ding J. Impact of PC/BCP Mutations on Seroconversion and Relapse in HBeAg-Positive Chronic Hepatitis B Patients Treated with Nucleoside Analogues. *Infect Drug Resist* 2025;18:5949–5959. doi:10.2147/IDR.S536426, PMID:41267799.
- [13] Hu Q, Zhang X, Cao X, Tao S, Chen C, Lu M, *et al*. Long-term effects of peginterferon-based therapy versus nucleos(t)ide analogue monotherapy in non-cirrhotic HBeAg-positive chronic hepatitis B patients. *Antiviral Res* 2025;240:106192. doi:10.1016/j.antiviral.2025.106192, PMID:40403849.