Journal of Clinical and Translational Hepatology **2025**
DOI: 10.14218/JCTH.2025.00252

Research Letter

Impact of Alanine Transaminase Thresholds on Treatment Eligibility of Patients with Chronic Hepatitis B: A Cross-sectional Study of the China Registry of Hepatitis B

Hao Wang[1,2], Xiaoqian Xu[1,2], Shan Shan[3], Yuemin Nan[4], Xiaoyuan Xu[5], Hui Zhuang[6], Hong You[3*], Jidong Jia[3*], Yuanyuan Kong[1,2*] and China Registry of Hepatitis B (CR-HepB) Group

[1]National Clinical Research Center for Digestive Disease, Beijing Friendship Hospital, Capital Medical University, Beijing, China; [2]Department of Clinical Epidemiology and Evidence-Based Medicine, Beijing Clinical Research Institute, Beijing, China; [3]Liver Research Center, State Key Lab of Digestive Health, Beijing Friendship Hospital, Capital Medical University, Beijing, China; [4]Department of Traditional and Western Medical Hepatology, Third Hospital of Hebei Medical University, Shijiazhuang, Hebei, China; [5]Department of Infectious Diseases, Peking University First Hospital, Beijing, China; [6]Department of Microbiology and Infectious Disease Center, Peking University Health Science Center, Beijing, China

Received: May 28, 2025 | **Revised:** July 02, 2025 | **Accepted:** July 23, 2025 | **Published online:** August 22, 2025

Citation of this article: Wang H, Xu X, Shan S, Nan Y, Xu X, Zhuang H, *et al*. Impact of Alanine Transaminase Thresholds on Treatment Eligibility of Patients with Chronic Hepatitis B: A Cross-sectional Study of the China Registry of Hepatitis B. J Clin Transl Hepatol 2025. doi: 10.14218/JCTH.2025.00252.

Hepatitis B virus (HBV) infection remains a major global health issue, with nearly 86 million people in China living with chronic hepatitis B (CHB).[1] Recommendations for antiviral treatment are based on a comprehensive assessment of serum HBV DNA levels, alanine transaminase (ALT) levels, severity of liver disease, and risk factors such as age and family history. Although ALT is a key indicator for initiating antiviral therapy, the treatment thresholds recommended by major international guidelines vary significantly. In 2024, the World Health Organization (WHO) published updated guidelines for CHB, recommending an upper limit of normal (ULN) for ALT of 30 U/L for males and 19 U/L for females.[2] The European Association for the Study of the Liver (EASL) 2017 guideline, and the Asia Pacific Association for the Study of the Liver (APASL) 2015 guideline defined a ULN for ALT of 40 U/L for both males and females.[3,4] The American Association for the Study of Liver Diseases (AASLD) 2016 guideline recommended 30/19 U/L for males/females, respectively,[5] and this ULN was increased to 35/25 U/L in the AASLD 2018 guideline.[6] East Asia expert opinions on expanding CHB anti-HBV treatment recommended a ULN for ALT of 30/19 U/L.[7] To date, the newest Chinese guidelines for preventing and treating CHB (2022 version) have greatly expanded antiviral therapy indications.[8] However, the updated Chinese CHB guideline does not specify an ALT treatment threshold. Given the ongoing controversy over optimal ALT treatment thresholds, this study investigated treatment eligibility rates in treatment-naïve CHB patients under different ALT thresholds using a nationwide Chinese real-world database.

This study was conducted using the China Registry of Hepatitis B (hereinafter referred to as CR-HepB), a nationwide web-based electronic platform established in 2012 across 55 hospitals in China.[9] Treatment-naïve CHB patients aged ≥18 years were included. Individuals missing key variables, including ALT, aspartate aminotransferase, platelet count, or HBV DNA values, were excluded from the final analysis. Patients diagnosed with other liver diseases were also excluded.

Liver fibrosis was estimated using non-invasive scores, including APRI and FIB-4. Two sets of APRI cut-off values for detecting significant fibrosis and cirrhosis were used: high cut-offs of 1.5 and 2.0 based on commonly used criteria, and low cut-offs of 0.5 and 1.0 as recommended by the updated WHO 2024 guidelines. The proportion of CHB patients eligible for antiviral therapy under five CHB clinical guidelines (WHO 2024, EASL 2017, APASL 2015, AASLD 2018, and China 2022 guidelines) was estimated. Four ALT treatment thresholds were applied in this study: 40 U/L, 35/25 U/L, 30/19 U/L, and regardless of ALT levels.

A total of 6,039 CHB patients were included; the participant selection flowchart is shown in Supplementary Fig. 1, and clinical characteristics are presented in Supplementary Table 1. As shown in Figure 1A, treatment eligibility rates were 72.40%, 51.98%, 28.27%, 44.81%, and 77.86% according to WHO 2024, EASL 2017, APASL 2015, AASLD 2018, and China 2022 guidelines, respectively. According to the updated Chinese 2022 guidelines, antiviral therapy is recommended for CHB patients with detectable serum HBV DNA and persistently elevated ALT levels. It is estimated that 73.56% of CHB patients would be eligible for antiviral treatment if the

*Correspondence to: Hong You, Beijing Key Laboratory of Translational Medicine on Liver Cirrhosis, Beijing Clinical Research Institute, Beijing 10050, China. ORCID: https://orcid.org/0000-0001-9409-1158. Tel: +86-10-63139017, E-mail: youhongliver@ccmu.edu.cn; Jidong Jia, Liver Research Center, Beijing Friendship Hospital, Capital Medical University; National Clinical Research Center for Digestive Diseases, Beijing 10050, China. ORCID: https://orcid.org/0000-0002-4673-8890. Tel: +86-10-63139816, E-mail: jia_jd@ccmu.edu.cn; Yuanyuan Kong, Department of Clinical Epidemiology and Evidence-based Medicine, Beijing Clinical Research Institute; Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China. ORCID: https://orcid.org/0000-0002-2586-1443. Tel: +86-10-63139362, E-mail: kongyy@ccmu.edu.cn.

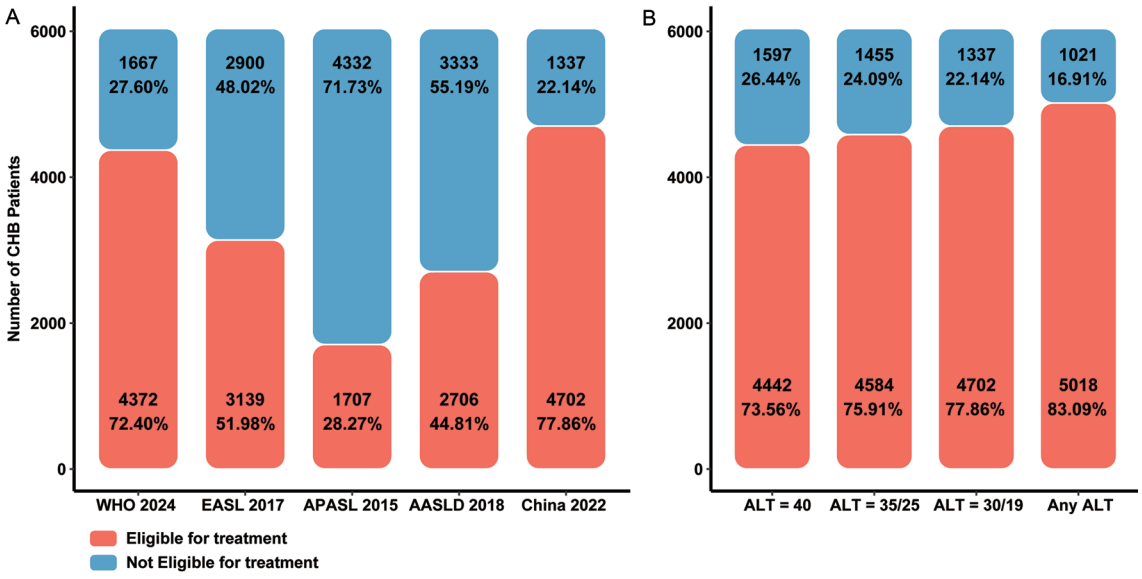

Fig. 1. Treatment eligibility rates for different clinical guidelines. (A) Bar plot showing the proportions of chronic hepatitis B patients eligible for antiviral treatment based on different clinical guidelines. (B) Number of chronic hepatitis B patients eligible for antiviral treatment based on different ALT levels. AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asia Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; WHO, World Health Organization.

ALT threshold is defined as 40 U/L (Fig. 1B). Treatment eligibility rates increase to 75.91%, 77.86%, and 83.09% when ALT thresholds are lowered to 35/25 U/L, 30/19 U/L, and regardless of ALT levels, respectively (Fig. 1B). Demographic and clinical characteristics of treatment-ineligible patients are shown in Table 1, Supplementary Table 2 and Supplementary Fig. 2. Among the 1,337 patients deemed ineligible per the China 2022 guideline, 211 (15.78%) had significant fibrosis, and 156 (11.67%) had cirrhosis.

According to the China 2022 guideline, a total of 1,021 CHB patients with undetectable HBV DNA were ineligible for antiviral treatment. Among 5,018 HBV DNA seropositive patients, 3,715 (61.52%) were older than 30 years, and 18 (0.30%) had a family history of hepatocellular carcinoma (HCC) or cirrhosis (Fig. 2). There were 1,285 (21.28%) HBV DNA seropositive patients aged ≤30 years without a family history; treatment eligibility for these patients should be determined based on ALT levels. Among these 1,285 patients, 709 would be eligible for antiviral treatment if the ALT threshold was 40 U/L (Fig. 2). A total of 1,285 (576 more) patients would be eligible if treated regardless of ALT levels (Fig. 2). Taken together, lowering the ALT treatment threshold is a feasible strategy to expand antiviral treatment, especially for HBV DNA seropositive CHB patients aged ≤30 years without a family history of HCC or cirrhosis.

To expand and simplify treatment criteria, especially for CHB patients in laboratory resource-limited areas, WHO updated the CHB guidelines in 2024.[2] Compared to the 2015 WHO guidelines, the most important update is the decrease in APRI cut-offs for significant fibrosis and cirrhosis from 1.5/2.0 to 0.5/1.0, respectively.[2] CHB patients with evidence of significant fibrosis or cirrhosis should receive antiviral treatment regardless of HBV DNA and ALT levels.[2] In this study, 1,124 (18.61%) patients had APRI >1.5, and 2,901 (48.04%) had APRI >0.5. This suggests that 1,777 more patients would be eligible for antiviral treatment under the updated WHO 2024 guidelines compared to 2015, highlighting a major expansion in treatment eligibility. Both the 2015 and 2024 WHO guidelines define ALT thresholds as 30/19 U/L, indicating WHO's consistent recommendation to lower ALT thresholds from the commonly used 40 U/L to 30/19 U/L.

Currently, accessibility and affordability of low-cost first-line antiviral agents have been significantly improved in China.[10] Cost-effectiveness studies showed that earlier implementation of expanded antiviral treatment with modified ALT thresholds can more efficiently prevent HBV-related complications.[11] As the most commonly used indicator of liver disease progression, decreasing ALT treatment thresholds and initiating antiviral therapy promptly have become a common understanding among clinicians and experts in China.[12] Growing evidence supports lower ALT treatment thresholds.[13,14] A meta-analysis found that approximately 30% of CHB patients with ALT <40 U/L had significant fibrosis.[13] Liu *et al*. found that 28.7% of HBV DNA seropositive CHB patients with ALT <35/25 U/L had significant inflammation.[14] Our previously published meta-analysis found that about 30% of untreated CHB patients with ALT <40 U/L had moderate to severe necroinflammation or significant fibrosis.[15] In this study, about 15.78% of patients with APRI >1.5 were ineligible for antiviral treatment. Taken together, a substantial proportion of CHB patients with ALT below current treatment thresholds remain at high risk for histological damage. While lowering ALT thresholds may expand treatment eligibility and improve disease control, the potential risks of overtreatment, especially among patients with a low risk of progression, must be carefully considered. Additionally, resource burden and cost-effectiveness should be thoroughly evaluated, particularly in low-resource settings where treatment access may be limited.

In the present study, we found that the treatment eligibility rate for all untreated CHB patients would increase by about 10% (from 73.56% to 83.09%) if the ALT treatment threshold were lowered from 40 U/L to no ALT threshold. This moderate increase is mainly because more than 60% of CHB patients are eligible for antiviral treatment regardless of ALT levels. Approximately 16.91% of CHB patients were ineligible for antiviral therapy due to undetectable HBV DNA levels. To further expand treatment eligibility, incorporating

Table 1. Characteristics of CHB patients who were ineligible for different clinical guidelines

	WHO 2024	EASL 2017	APASL 2015	AASLD 2018	China 2022
No. of patients, n (%)	1,667 (27.60)	2,900 (48.02)	4,332 (71.73)	3,333 (55.19)	1,337 (22.14)
Age, n (%)					
≤30 years	364 (21.84)	709 (24.45)	995 (22.97)	937 (28.11)	424 (31.71)
30–59 years	1,161 (69.65)	1,908 (65.79)	2,961 (68.35)	2,175 (65.26)	757 (56.62)
≥60 years	142 (8.52)	283 (9.76)	376 (8.68)	221 (6.63)	156 (11.67)
Male, n (%)	1,000 (59.99)	1,588 (54.76)	2,548 (58.82)	2,041 (61.24)	798 (59.69)
HBeAg positive, n (%)	369 (22.14)	246 (8.48)	1,225 (28.28)	938 (28.14)	328 (24.53)
ALT, U/L	20.00 (16.00–26.00)	26.00 (19.00–35.00)	30.00 (21.00–45.00)	30.00 (21.00–44.00)	25.00 (17.00–43.00)
AST, U/L	21.00 (18.00–25.00)	25.00 (20.00–33.00)	26.50 (21.00–35.00)	26.90 (21.30–35.00)	25.00 (19.40–43.40)
PLT, $\times 10^9$/L	207.14 ± 55.02	183.93 ± 69.31	192.45 ± 70.12	188.71 ± 65.56	173.44 ± 74.48
ALB, g/L	43.41 ± 8.55	42.88 ± 12.47	42.87 ± 11.41	42.61 ± 9.13	42.92 ± 15.95
TBiL, μmol/L	13.47 (9.93–18.40)	14.10 (10.10–20.10)	13.60 (10.10–18.70)	13.55 (10.08–18.50)	16.40 (11.00–25.50)
HBV-DNA, n (%)					
<2,000 IU/mL	757 (45.41)	1,261 (43.48)	1,280 (29.55)	500 (15.00)	1,040 (77.79)
2,000–19,999 IU/mL	363 (21.78)	649 (22.38)	962 (22.21)	881 (26.43)	59 (4.41)
≥20,000 IU/mL	547 (32.81)	990 (34.14)	2,090 (48.25)	1,952 (58.57)	238 (17.80)
APRI WHO 2024 Criteria					
>0.5, n (%)	0 (0)	842 (29.03)	1,276 (29.46)	941 (28.23)	538 (40.24)
>1.0, n (%)	0 (0)	409 (14.10)	318 (7.34)	375 (11.25)	325 (24.31)
APRI WHO 2015 Criteria					
>1.5, n (%)	0 (0)	254 (8.76)	16 (0.37)	238 (7.14)	211 (15.78)
>2.0, n (%)	0 (0)	179 (6.17)	9 (0.21)	162 (4.86)	156 (11.67)
FIB-4 >3.25, n (%)	10 (0.60)	391 (13.48)	37 (0.85)	324 (9.72)	289 (21.62)

AASLD, American Association for the Study of Liver Diseases; ALB, albumin; ALT, alanine aminotransferase; APASL, Asia Pacific Association for the Study of the Liver; APRI, AST to PLT ratio index; AST, aspartate transaminase; EASL, European Association for the Study of the Liver; PLT, platelet count; TBiL, total bilirubin; WHO, World Health Organization.

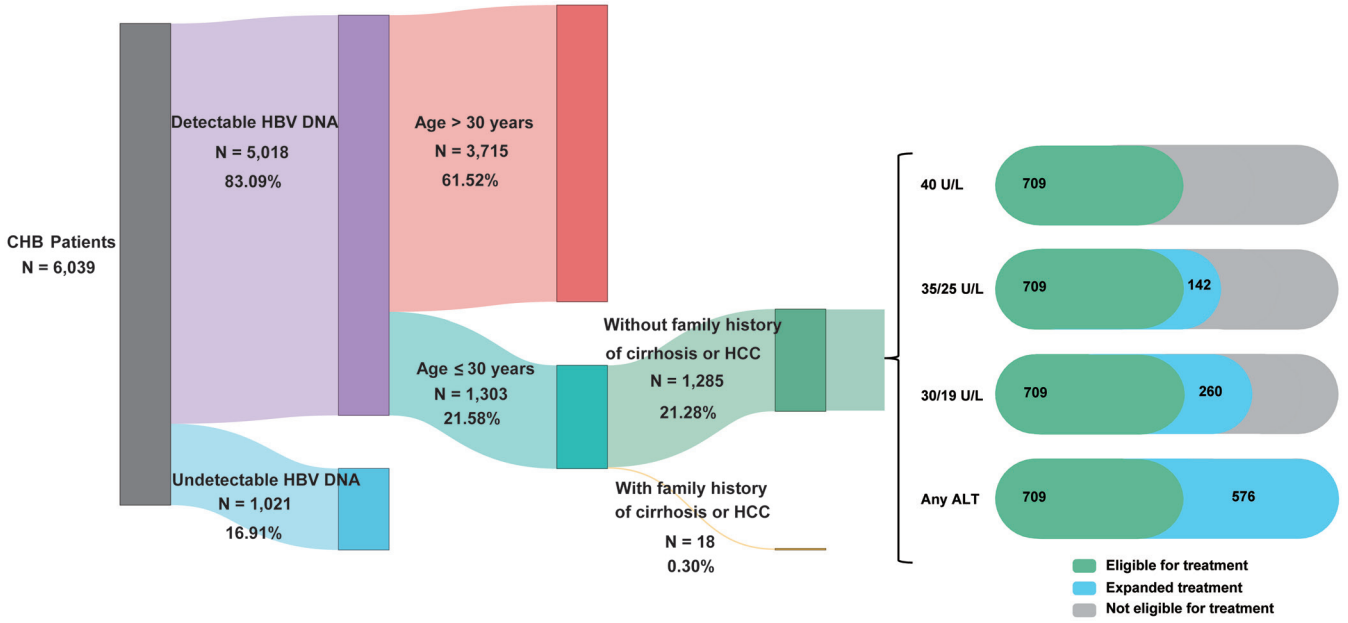

Fig. 2. Proportions of chronic hepatitis B patients eligible for antiviral treatment according to different treatment criteria. The Sankey plot shows the proportions of chronic hepatitis B patients eligible for antiviral treatment. ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

non-invasive tests such as APRI and FIB-4 scores into treatment criteria could be a preferable option.

Several limitations of this study should be noted. First, the cross-sectional design limits our ability to evaluate longitudinal outcomes such as disease progression and clinical endpoints. Future prospective studies are warranted to track patients over time and assess the long-term impact of different ALT thresholds, providing more definitive evidence to guide clinical decision-making. Second, we used non-invasive APRI and FIB-4 scores to assess significant fibrosis and cirrhosis because FibroScan and histological data were unavailable in the database. Finally, data on quality of life, adverse events, and patient preferences were not available in the CR-HepB database, limiting our ability to fully assess the patient-centered impact of different treatment strategies. Future research incorporating these dimensions is needed for a more comprehensive evaluation.

In conclusion, the newest WHO 2024 guideline and China 2022 guideline significantly expand antiviral treatment eligibility rates for CHB patients compared to other international clinical guidelines. Lowering ALT treatment thresholds is an effective strategy to broaden CHB antiviral treatment, especially for HBV DNA seropositive patients aged ≤30 years without a family history of HCC or cirrhosis.

Acknowledgments

The authors acknowledge the participants and their families who contributed to making this study possible.

Funding

This work was partially supported by research grants from the National Key Research and Development Program, China (2023YFC2306902, 2023YFC2306900), High-level Public Health Technical Talents of the Beijing Municipal Health Commission, China (XUEKEGUGAN-010-018), Beijing Municipal Administration of Hospitals Incubating Program (PX2024003), and Research Grant of Capital Medical University (PYZ21051, PYZ23073).

Conflict of interest

JJ has been an Executive Associate Editor of *Journal of Clinical and Translational Hepatology* since 2016. YN and HY have been Editorial Board Members of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Conception and design (JJ, HY, YK), data collection and cleaning (HW, XqX, SS, YN, XyX), data analysis (HW), drafting of the manuscript (HW), and critical revision of the manuscript (HZ, HY, JJ, YK). All authors read and approved the final manuscript.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2024) and approved by the Beijing Friendship Hospital Ethics Committee, Capital Medical University (BJFH-EC/2014-044). Informed consent was waived.

Data sharing statement

All data analyzed in this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding authors. Supplementary materials related to this article can be found at the website of the article.

References

[1] Liu J, Zhang S, Wang Q, Shen H, Zhang M, Zhang Y, *et al*. Seroepidemiology of hepatitis B virus infection in 2 million men aged 21-49 years

in rural China: a population-based, cross-sectional study. Lancet Infect Dis 2016;16(1):80–86. doi:10.1016/S1473-3099(15)00218-2, PMID:26268687.
[2] World Health Organization. Guidelines for the Prevention, Diagnosis, Care and Treatment for People with Chronic Hepatitis B Infection (Text Extract): Executive Summary. Infect Dis Immun 2024;4(3):103–105. doi:10.1097/ID9.0000000000000128, PMID:39391287.
[3] European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370–398. doi:10.1016/j.jhep.2017.03.021, PMID:28427875.
[4] Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, *et al*. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10(1):1–98. doi:10.1007/s12072-015-9675-4, PMID:26563120.
[5] Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH, *et al*. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63(1):261–283. doi:10.1002/hep.28156, PMID:26566064.
[6] Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, *et al*. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67(4):1560–1599. doi:10.1002/hep.29800, PMID:29405329.
[7] Kao JH, Hu TH, Jia J, Kurosaki M, Lim YS, Lin HC, *et al*. East Asia expert opinion on treatment initiation for chronic hepatitis B. Aliment Pharmacol Ther 2020;52(10):1540–1550. doi:10.1111/apt.16097, PMID:32951256.
[8] 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.
[9] Shan S, You H, Niu J, Shang J, Xie W, Zhang Y, *et al*. Baseline Characteristics and Treatment Patterns of the Patients Recruited to the China Registry of Hepatitis B. J Clin Transl Hepatol 2019;7(4):322–328. doi:10.14218/JCTH.2019.00052, PMID:31915601.
[10] Zhao X, Li M, Wang H, Xu X, Wu X, Sun Y, *et al*. Impact of National Centralized Drug Procurement Policy on Antiviral Utilization and Expenditure for Hepatitis B in China. J Clin Transl Hepatol 2022;10(3):420–428. doi:10.14218/JCTH.2022.00167, PMID:35836769.
[11] Zhang S, Wang C, Liu B, Lu QB, Shang J, Zhou Y, *et al*. Cost-effectiveness of expanded antiviral treatment for chronic hepatitis B virus infection in China: an economic evaluation. Lancet Reg Health West Pac 2023;35:100738. doi:10.1016/j.lanwpc.2023.100738, PMID:37424693.
[12] Chinese Society of Hepatology, Chinese Medical Association. Expert opinion on expanding anti-HBV treatment for chronic hepatitis B. Zhonghua Gan Zang Bing Za Zhi 2022;30(2):131–136. doi:10.3760/cma.j.cn501113-20220209-00060, PMID:35359064.
[13] Zhang C, Li JW, Wu Z, Zhao H, Wang GQ. Significant Histologic Changes Are Not Rare in Treatment-naive Hepatitis B Patients with Normal Alanine Aminotransferase Level: A Meta-analysis. J Clin Transl Hepatol 2021;9(5):615–625. doi:10.14218/JCTH.2020.00136, PMID:34722176.
[14] Liu J, Wang J, Yan X, Xue R, Zhan J, Jiang S, *et al*. Presence of Liver Inflammation in Asian Patients With Chronic Hepatitis B With Normal ALT and Detectable HBV DNA in Absence of Liver Fibrosis. Hepatol Commun 2022;6(4):855–866. doi:10.1002/hep4.1859, PMID:34783181.
[15] Li S, Shi L, Xu X, Wang H, You H, Jia J, *et al*. Systematic review with meta-analysis: Significant histological changes among treatment-naïve chronic hepatitis B patients with normal alanine aminotransferase levels by different criteria. Aliment Pharmacol Ther 2023;58(7):648–658. doi:10.1111/apt.17658, PMID:37551720.