



Original Article



Baseline Liver Fibrosis Severity Predicts Superior HBeAg Clearance and Fibrosis Reversal following Peg-IFN α plus Nucleos(t)ide Analog Therapy in HBeAg-positive Chronic Hepatitis B Patients

Yaqin Zhang^{1,2#}, Fengxin Chen^{1,3#}, Shuojie Wang^{1#}, Xin Wei¹, Shiyu Wang¹, Linmei Yao¹, Zixuan Gao¹, Wen Deng¹ and Minghui Li^{1,2,4*}

¹Department of Hepatology Division 2, Beijing Ditan Hospital, Capital Medical University, Beijing, China; ²HBV Infection, Clinical Cure and Immunology Joint Laboratory for Clinical Medicine, Capital Medical University, Beijing, China; ³Hepatology Center, Beijing Ditan Hospital, Capital Medical University, Beijing, China; ⁴Department of Hepatology Division 2, Peking University Ditan Teaching Hospital, Beijing, China

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Abstract

Background and Aims: The impact of baseline liver fibrosis severity on the effectiveness of pegylated interferon (Peg-IFN) combined with nucleos(t)ide analogs (NAs) in the treatment of hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) has not been fully clarified. This study aimed to investigate whether the effectiveness of this combination therapy differed according to the severity of baseline liver fibrosis. **Methods:** A total of 172 HBeAg-positive CHB patients receiving Peg-IFN plus NAs were stratified according to non-invasive fibrosis markers (aspartate aminotransferase-to-platelet ratio index [APRI] and fibrosis-4 index [FIB-4]) into three groups: no significant fibrosis (n = 75), significant fibrosis (n = 70), and advanced fibrosis/cirrhosis (n = 27). The primary outcome was the HBeAg clearance rate at 24 months of treatment. Secondary outcomes included the hepatitis B surface antigen (HBsAg) clearance rate, the rate of HBsAg level decline > 1.0 log₁₀, virological response, and improvement in non-invasive fibrosis indices. **Results:** At 24 months, HBsAg clearance and complete virological response rates were comparable across the three groups. Cumulative HBeAg clearance rates differed significantly (log-rank *P* = 0.027): 16.00%, 30.00%, and 40.74% in the three groups, respectively, with Group 3 higher than Groups 1 and 2. Multivariate analysis identified a significantly higher likelihood of HBeAg clearance in Group 3 versus Group 1 (adjusted odds ratio = 6.373, 95% confidence interval: 1.288–31.531, *P* = 0.023). Additionally, analysis of liver fibrosis outcomes showed that patients with more severe baseline fibrosis had a higher proportion of improvement in non-invasive fibrosis indices, with 95.00% in Group 3, while 42.98% of the overall

cohort achieved fibrosis improvement. **Conclusions:** Baseline fibrosis severity is associated with higher HBeAg clearance and greater improvement in non-invasive fibrosis indices during Peg-IFN plus NAs therapy in HBeAg-positive CHB.

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Introduction

Chronic hepatitis B virus (HBV) infection is a major global public health challenge. Worldwide, an estimated 254 million people are living with chronic HBV infection, leading to more than 800,000 deaths each year from related complications such as cirrhosis and hepatocellular carcinoma (HCC), according to World Health Organization estimates.¹ In China, the burden of chronic hepatitis B (CHB) is particularly heavy. Therefore, optimizing treatment strategies to improve the long-term prognosis of patients has always been a core goal in clinical practice and research.

For patients with hepatitis B e antigen (HBeAg)-positive CHB, HBeAg seroconversion represents an important intermediate treatment endpoint, linked to improved liver histology and a reduction in long-term hepatic risks such as cirrhosis and HCC.² The impact of different antiviral agents on clinical outcomes (e.g., HCC incidence) varies.³ Currently, the combination of pegylated interferon (Peg-IFN) and nucleos(t)ide analogs (NAs), by synergistically exerting immunomodulatory and potent antiviral effects, has become an important strategy in pursuit of clinical cure, such as hepatitis B surface antigen (HBsAg) clearance.^{4–7} However, the clinical response to this regimen shows significant individual heterogeneity, and the influencing factors need to be further elucidated.

Baseline liver fibrosis stage is a core indicator reflecting

Keywords: Chronic hepatitis B; Liver fibrosis; Treatment effectiveness; HBeAg; APRI; FIB-4.

*Contributed equally to this work.

Correspondence to: Minghui Li, Department of Hepatology Division 2, Beijing Ditan Hospital, Capital Medical University, Beijing 100015, China. ORCID: <https://orcid.org/0000-0003-3233-5473>. E-mail: wuhm2000@sina.com.

long-term liver damage and pathological remodeling. The formation of liver fibrosis involves not only the activation of hepatic stellate cells but also the participation of various immune cells such as macrophages, natural killer cells, T lymphocytes, and B lymphocytes through complex intercellular communication, collectively regulating the progression or regression of fibrosis.⁸ This dynamic immune microenvironment may directly affect the body's response efficiency to subsequent antiviral therapy, especially therapies primarily based on immune modulation. Currently, non-invasive fibrosis assessment indices such as aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) are widely used in clinical research and patient stratification due to their convenience and good reproducibility.^{9–11} Previous studies have indicated that Peg-IFN may have unique advantages in delaying or even reversing liver fibrosis,¹² and patients with advanced fibrosis who have lower liver stiffness measurement values early in treatment show more significant fibrosis improvement.¹³ Moreover, sustained antiviral therapy helps reduce the risk of cirrhosis in HBeAg-negative CHB patients.¹⁴ However, these studies mostly focus on fibrosis regression itself or lack refined stratification based on baseline fibrosis severity.

Currently, there is a lack of systematic evidence regarding the direct impact of different baseline liver fibrosis severities (especially those distinguished by APRI/FIB-4 as no significant fibrosis, significant fibrosis, and early cirrhosis) on the effectiveness of the Peg-IFN combined with NAs regimen in treating HBeAg-positive CHB patients. Clarifying this association is crucial for identifying optimal patient populations, predicting treatment responses, and formulating individualized strategies in clinical practice.

Therefore, this retrospective cohort study aimed to stratify HBeAg-positive CHB patients according to baseline APRI and FIB-4 indices and to compare the effectiveness of Peg-IFN plus NAs across different fibrosis stages, particularly regarding HBeAg clearance and liver fibrosis regression, thereby providing evidence to guide individualized treatment strategies.

Methods

We conducted a retrospective cohort study of HBeAg-positive CHB patients who initiated Peg-IFN plus NAs therapy at Beijing Ditan Hospital, Capital Medical University, from January 2022 to December 2023. Patients with missing baseline data or substantial missing dynamic data during treatment were excluded from the analysis. The treatment regimen consisted of Peg-IFN (180 µg/weekly) combined with either tenofovir disoproxil fumarate or tenofovir alafenamide, with treatment duration varying according to clinical response and tolerance.

Inclusion and exclusion criteria

Inclusion criteria: (1) Age 18–65 years; (2) diagnosis of CHB (2019 guideline); (3) HBsAg and HBeAg positivity > 6 months; (4) treatment with Peg-IFN + NAs. Exclusion criteria: (1) HCV/HDV/HIV co-infection; (2) decompensated cirrhosis or HCC; (3) autoimmune or alcoholic liver disease; (4) pregnancy or lactation; (5) severe cardiac or renal dysfunction.

Grouping criteria and evaluation indicators

We stratified patients into three groups according to their baseline non-invasive fibrosis indices. To ensure rigorous classification, clinical fibrosis stages were defined based on established cutoff values for APRI and FIB-4, which have been validated in CHB patients against liver biopsy and are widely applied in clinical studies for fibrosis assessment.^{15,16}

It should be emphasized that these groupings represent study-specific, non-invasive stratification for comparative analyses of treatment response and do not correspond to histological fibrosis stages. "No significant fibrosis" (Stage A) corresponded to APRI ≤ 0.5 and FIB-4 ≤ 1.45; "Significant fibrosis" (Stage B) corresponded to APRI 0.5–1.5 or FIB-4 1.45–3.25; and the "Advanced fibrosis/cirrhosis" (Stage C) corresponded to APRI > 1.5 or FIB-4 > 3.25. In cases of discordance between the two indices, patients were assigned to the group corresponding to the higher fibrosis stage. Consequently, the cohort was divided into: Group 1 (no significant fibrosis, *n* = 75); Group 2 (significant fibrosis, *n* = 70); and Group 3 (advanced fibrosis/cirrhosis, *n* = 27).

Because APRI and FIB-4 incorporate alanine aminotransferase (ALT), higher baseline ALT in Group 3 could overestimate fibrosis and affect virological outcomes such as HBeAg clearance. To account for this, baseline ALT was included as a covariate in all multivariate analyses evaluating treatment response. Fibrosis outcomes were interpreted in conjunction with ALT and aspartate aminotransferase (AST) levels to ensure accurate classification.

The primary outcome was the HBeAg clearance rate at 24 months of treatment. Secondary outcomes included HBeAg seroconversion, defined as loss of HBeAg with the appearance of anti-HBe antibodies; the rate of HBsAg decline > 1.0 log₁₀ IU/mL; HBsAg clearance rate; virological response (HBV DNA < 20 IU/mL); and liver fibrosis outcomes.

For the assessment of fibrosis outcomes, dynamic changes were evaluated in 114 patients who had discontinued interferon treatment for at least 3 months at the time of the month 24 assessment. Changes were determined by comparing the predefined fibrosis stages (Stage A, B, or C) at baseline versus month 24. Outcomes were categorized into three grades: Progression, defined as an increase in fibrosis stage (e.g., from Stage A to B/C, or B to C); Stable, no change in fibrosis stage; Improvement, a decrease in fibrosis stage (e.g., from Stage C to B/A, or B to A).

Statistical methods

All data were analyzed using SPSS software (version 25.0). Continuous data are presented as mean ± standard deviation or median (interquartile range, IQR), with intergroup differences assessed by one-way ANOVA or the Kruskal–Wallis *H* test, respectively. Categorical data, expressed as number (percentage), were compared using the χ^2 test or Fisher's exact test. Independent predictors of HBeAg clearance were identified via multivariate logistic regression. Baseline ALT was additionally included as a covariate in the multivariate model, even though its association with HBeAg clearance was not significant in univariate analysis (*P* > 0.1), to account for its potential confounding effect. The Kaplan–Meier method was used to estimate cumulative HBeAg clearance rates over the 24-month follow-up. The event was defined as confirmed HBeAg loss during follow-up. Since all patients completed 24 months of observation, no censoring was required. Groups were compared using the log-rank test. Statistical significance was set at *P* < 0.05.

Sensitivity analysis

Considering that some patients might not complete the full course of treatment due to intolerance or other reasons, a sensitivity analysis was conducted. We restricted the analysis to patients who received interferon therapy for ≥ 6 months (*n* = 150) to evaluate whether the main conclusions remained robust in this subgroup of patients who completed a minimum treatment duration. The baseline characteristics, efficacy evaluations, and statistical analysis methods in this

subgroup were consistent with those in the full analysis set ($n = 172$). Multivariate analyses adjusting for baseline ALT were also performed in this subgroup to confirm the robustness of the main findings.

Results

Baseline characteristics of the study population

A total of 172 patients who completed 24 months of treatment follow-up were included in the final analysis. This cohort consisted of 95 males (55.23%) and 77 females (44.77%), with a mean age of 39.05 ± 8.29 years. Regarding treatment history, there were 91 treatment-naïve patients and 81 treatment-experienced patients. Among them, 35 patients received tenofovir disoproxil fumarate combined with Peg-IFN α , while 137 patients received tenofovir alafenamide combined with Peg-IFN α . Peg-IFN α treatment durations varied from 1 to 24 months, with 150 patients receiving treatment for more than 6 months. Their baseline characteristics are summarized in Table 1.

Based on baseline APRI and FIB-4 indices, the patients were categorized into three groups: Group 1 (no significant fibrosis, $n = 75$), Group 2 (significant fibrosis, $n = 70$), and Group 3 (advanced fibrosis/cirrhosis, $n = 27$). As shown in Figure 1 and Table 1, there were no significant differences among the three groups in age or sex distribution ($P > 0.05$). Additionally, no significant differences were observed in baseline HBsAg levels, HBeAg levels, or the proportion of patients with HBsAg $< 1,500$ IU/mL across groups. However, compared with Group 1, patients in Group 2 and Group 3 had significantly higher baseline ALT and AST levels and significantly lower platelet (PLT) counts (all $P < 0.05$). In addition, the proportion of treatment-naïve patients and HBV DNA-positive patients was higher in the advanced fibrosis/cirrhosis, indicating potential baseline imbalance across groups.

Comparison of antiviral treatment effectiveness among different fibrosis groups at 12 and 24 months

After 24 months of antiviral treatment, all patients showed a continuous decline in HBsAg levels, indicating a positive effect of the treatment regimen on suppressing HBsAg. As shown in Figure 2, Table 2, and Supplementary Table 1, HBsAg levels in Group 2 were significantly lower than those in Group 1 at both 12 and 24 months of treatment ($P < 0.05$). Furthermore, the proportion of patients in Group 2 achieving an HBsAg decline $> 1.0 \log_{10}$ within 12 months was significantly higher than that in Group 1 ($P < 0.01$). Nevertheless, there were no notable differences among the three groups regarding the rate of HBsAg clearance or the rate of undetectable HBV DNA.

Regarding HBeAg serological response, differences in HBeAg clearance rates were observed among the three groups at both 12 and 24 months. At 12 months, the HBeAg clearance rates for Group 1, Group 2, and Group 3 were 5.48% (4/73), 14.71% (10/68), and 29.63% (8/27), respectively. Group 3 exhibited a significantly higher clearance rate compared with Group 1 ($P = 0.006$). At 24 months, the HBeAg clearance rates were 16.00% (12/75) for Group 1, 30.00% (21/70) for Group 2, and 40.74% (11/27) for Group 3. Both Group 2 and Group 3 showed significantly higher HBeAg clearance rates compared with Group 1 ($P = 0.022$).

In addition, HBeAg seroconversion rates were analyzed and summarized in Table 2. At 12 months, seroconversion occurred in 10.96% of patients in Group 1, 10.29% in Group 2, and 25.93% in Group 3, with a trend toward higher seroconversion in patients with more advanced fibrosis, al-

though the difference did not reach statistical significance ($P = 0.097$). At 24 months, seroconversion rates were 14.67%, 11.43%, and 18.52% in Groups 1, 2, and 3, respectively ($P = 0.647$). These results indicate that while HBeAg clearance is significantly influenced by baseline fibrosis severity, HBeAg seroconversion rates showed a trend but did not reach statistical significance.

Subgroup analysis according to treatment history

Subgroup analyses were conducted in treatment-naïve and treatment-experienced patients (Supplementary Table 2).

In treatment-naïve patients, HBeAg clearance at 24 months tended to increase with baseline fibrosis severity: 15.15% (no significant fibrosis), 23.68% (significant fibrosis), and 35.0% (advanced fibrosis/cirrhosis). HBeAg seroconversion was low across groups (13%–25%), while HBsAg decline $> 1.0 \log_{10}$ IU/mL was highest in the significant fibrosis group. HBsAg clearance was comparable across fibrosis groups. The proportions of patients with HBV DNA < 20 IU/mL at baseline and at month 24 were similar among the three fibrosis groups, indicating comparable virological responses within this subgroup.

In treatment-experienced patients, similar trends were observed: HBeAg clearance increased from 19.05% to 57.14% with fibrosis severity, HBeAg seroconversion remained low, HBsAg decline showed a trend with fibrosis severity, and HBsAg clearance was similar across groups. Within these patients, the rates of HBV DNA < 20 IU/mL at baseline and at month 24 were also comparable among fibrosis groups, suggesting consistent virological responses across fibrosis strata.

Overall, trends in both subgroups were broadly consistent with the total cohort (Table 2), indicating that baseline fibrosis severity was associated with HBeAg and HBsAg responses, while HBV DNA suppression remained similar across fibrosis groups regardless of prior treatment history.

Univariate regression analysis of factors influencing HBeAg clearance at 24 months of treatment

Univariate logistic regression analysis was performed to determine which clinical factors predicted HBeAg clearance at 24 months of treatment. As shown in Supplementary Table 3, several baseline and on-treatment indicators were significantly associated with HBeAg clearance ($P < 0.1$) and were subsequently identified as candidates for multivariable analysis. It is important to note that neither treatment history (naïve vs. experienced, $P = 0.426$) nor baseline ALT ($P = 0.310$) or AST ($P = 0.490$) levels showed a statistically significant association with HBeAg clearance in this cohort.

Baseline factors: Patients with more severe liver fibrosis had a higher likelihood of achieving HBeAg clearance. The odds ratios (ORs) in Group 2 and Group 3 were 2.249 (95% confidence interval [CI]: 1.009–5.015) and 3.609 (95% CI: 1.348–9.667) times that of Group 1, respectively. Patients with baseline HBsAg $< 1,500$ IU/mL had a 3.261-fold higher likelihood of clearance than those with HBsAg $\geq 1,500$ IU/mL (95% CI: 1.579–6.732). A lower baseline HBeAg level (OR = 0.999, 95% CI: 0.998–1.000) was favorable for HBeAg clearance.

Dynamic on-treatment indicators: Lower HBeAg levels at months 3, 6, 9, and 12 were all associated with a higher likelihood of HBeAg clearance at 24 months (all $P < 0.05$). Higher APRI at month 3 (OR = 1.140, $P = 0.085$) and month 9 (OR = 1.271, $P = 0.070$) showed marginally significant associations with increased clearance probability. Patients who achieved HBeAg clearance by month 12 had a significantly higher probability of maintaining it at month 24 (OR = 53.478, 95% CI: 11.694–244.567). HBsAg clearance at

Table 1. Baseline clinical characteristics stratified by fibrosis stage

Variable	Group 1: No significant fibrosis (n = 75)	Group 2: Significant fibrosis (n = 70)	Group 3: Advanced fibrosis/cirrhosis (n = 27)	Test statistic	P
Demographic characteristics					
Age, years	38.01 ± 8.06	40.10 ± 8.32	39.19 ± 8.81	1.153	0.318
Male, n (%)	44 (58.67)	36 (51.43)	15 (55.56)	0.769	0.681
Treatment-naïve (%)	33 (44.00)	38 (54.29)	20 (74.07)	7.297	0.026*
TDF + Peg-IFNa (%)	10 (13.33)	17 (24.29)	8 (29.63)	4.382	0.112
TAF + Peg-IFNa (%)	65 (86.67)	53 (75.71)	19 (70.37)		
Weeks of Peg-IFNa treatment	12.15 ± 5.96	12.36 ± 6.80	11.52 ± 7.42	0.16	0.852
Virological characteristics					
HBsAg < 1,500 IU/mL, n (%)	16 (21.33)	25 (35.71)	8 (29.63)	3.696	0.158
HBV DNA positive, n (%)	30 (40.00)	41 (58.57)	21 (77.78)	12.615	0.002**
HBsAg, log10, IU/mL	3.71 (3.24, 4.08)	3.58 (2.78, 4.14)	3.73 (2.95, 4.64)	1.34	0.512
HBeAg, S/CO	31.090 (4.1, 475.8)	95.736 (5.9, 1,003.4)	91.760 (3.7, 813.2)	0.978	0.613
Clinical and laboratory parameters					
Alanine aminotransferase, U/L	22.200 (15.6, 39.8)	58.750 (37.4, 85.4)	135.400 (74.1, 203.6)	78.718	0.001**
Aspartate aminotransferase, U/L	19.000 (17.0, 24.9)	45.800 (33.3, 56.2)	84.000 (61.3, 124.0)	115.45	0.001**
Albumin, g/L	46.600 (44.2, 49.2)	45.500 (43.2, 46.8)	44.500 (41.2, 46.5)	15.052	0.001**
Alpha-fetoprotein, ng/mL	2.220 (1.8, 3.1)	3.190 (2.4, 4.7)	3.590 (2.8, 12.5)	26.591	0.001**
Hematological parameters					
White blood cell count, ×10 ⁹ /L	5.48 ± 1.43	4.02 ± 1.43	3.64 ± 1.49	25.542	0.001**
Neutrophil percentage, %	56.13 ± 9.29	53.60 ± 9.96	51.69 ± 11.74	2.345	0.099
Lymphocyte percentage, %	34.90 ± 8.55	36.24 ± 9.33	38.24 ± 11.08	1.326	0.268
Red blood cell count, ×10 ¹² /L	4.950 (4.5, 5.3)	4.695 (4.3, 5.0)	4.610 (4.3, 5.0)	11.32	0.003**
Hemoglobin, g/L	146.000 (134.0, 159.0)	140.000 (128.5, 155.0)	140.000 (132.0, 153.0)	4.34	0.114
Platelet count, ×10 ⁹ /L	222.000 (197.0, 265.0)	149.500 (125.8, 184.8)	104.000 (72.0, 127.0)	81.023	0.001**
Non-invasive fibrosis indices					
APRI	0.255 (0.2, 0.3)	0.847 (0.6, 1.1)	2.243 (1.8, 3.7)	138.712	0.001**
FIB-4	0.669 (0.5, 0.9)	1.512 (1.2, 2.0)	3.208 (2.4, 4.3)	116.798	0.001**

TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; Peg-IFNa, pegylated interferon-alpha; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; HBeAg, hepatitis B e antigen; IU/mL, international units per milliliter; S/CO, signal-to-cutoff ratio; U/L, units per liter; g/L, grams per liter; ng/mL, nanograms per milliliter; APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index. * $P < 0.05$; ** $P < 0.01$.

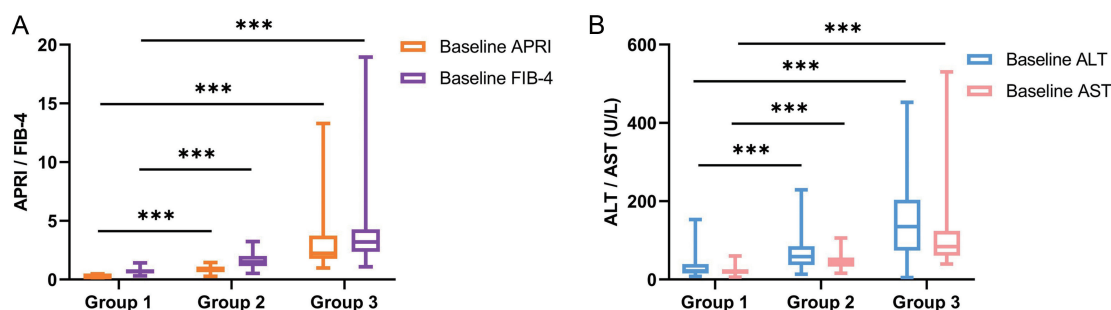


Fig. 1. Baseline non-invasive fibrosis indices and aminotransferase levels among different fibrosis groups. (A) Baseline APRI and FIB-4 values among the three fibrosis groups. (B) Baseline ALT and AST levels among the three fibrosis groups. Group 1, no significant fibrosis; Group 2, significant fibrosis; Group 3, advanced fibrosis/cirrhosis group. *** $P < 0.001$. APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; U/L, units per liter.

month 12 was also a strong predictor of HBeAg clearance at 24 months (OR = 13.158, 95% CI: 1.427–121.292).

In summary, more severe baseline liver fibrosis, lower baseline viral antigen levels, rapid early decline in HBeAg during treatment, and achieving HBeAg or HBsAg clearance by month 12 were favorable predictive factors for HBeAg clearance at 24 months.

Multivariate analysis of factors influencing HBeAg clearance at 24 months of treatment

To further identify independent predictive factors for HBeAg clearance, a multivariate logistic regression analysis was performed incorporating variables including baseline HBsAg grouping, APRI value at month 3, HBeAg level at month 6, and baseline fibrosis grouping. Baseline ALT was included as

a covariate to account for potential confounding (due to only 44 patients achieving HBeAg clearance, no additional variables were included to avoid overfitting). The overall goodness-of-fit of the model was Nagelkerke $R^2 = 0.224$.

As shown in Figure 3 and Supplementary Table 4, after adjusting for other factors, baseline fibrosis severity and the HBeAg level at month 6 of treatment were identified as independent predictors of HBeAg clearance at 24 months (both $P < 0.05$). Specifically, compared with Group 1, the OR for achieving HBeAg clearance in Group 3 was 6.373 (95% CI: 1.288–31.531, $P = 0.023$), indicating that more severe baseline fibrosis is an independent favorable factor for HBeAg clearance. For each 1 signal-to-cutoff ratio (S/CO) decrease in HBeAg level at month 6, the OR for HBeAg clearance increased correspondingly (OR = 0.997, 95% CI:

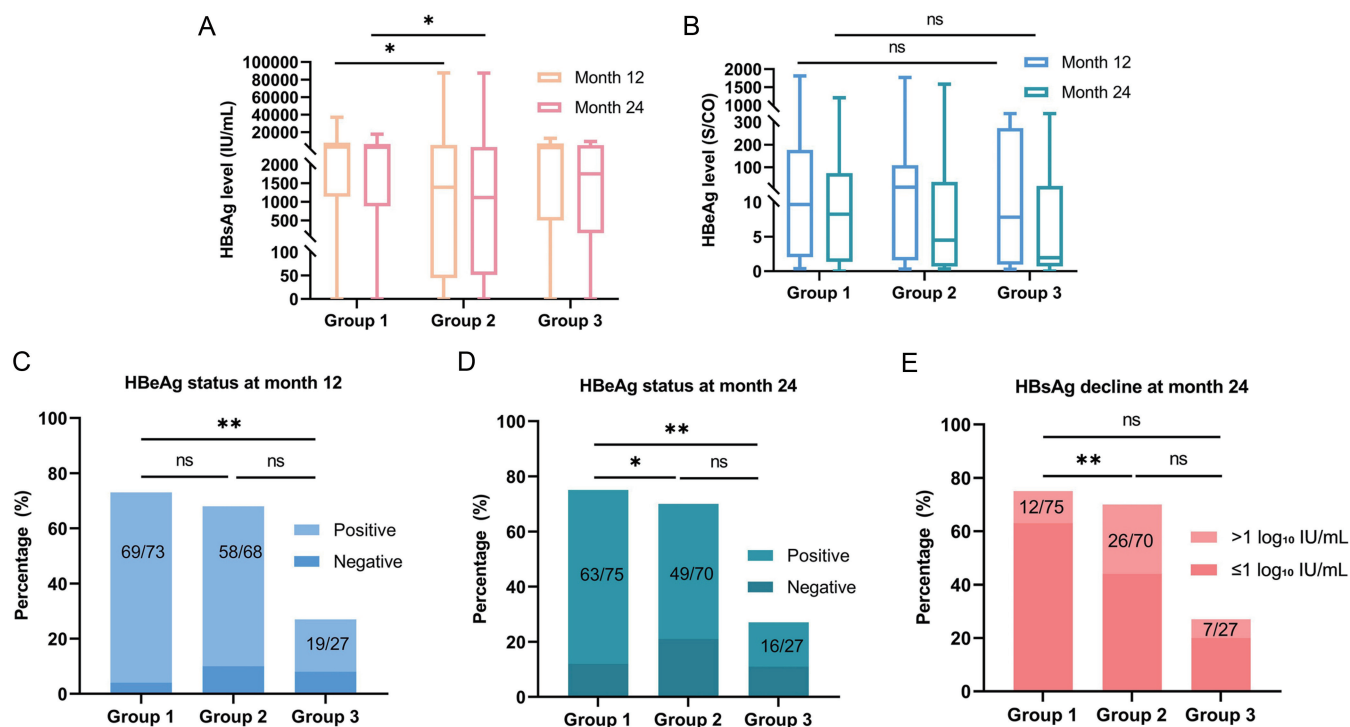


Fig. 2. Comparison of therapeutic effects among different fibrosis groups at 12 and 24 months of antiviral treatment. (A) HBsAg levels at months 12 and 24. (B) HBeAg levels at months 12 and 24. (C) HBsAg status at month 12. (D) HBeAg status at month 24. (E) HBsAg decline at month 24. Group 1, no significant fibrosis; Group 2, significant fibrosis; Group 3, advanced fibrosis/cirrhosis group. * $P < 0.05$; ** $P < 0.01$. The y-axes in panels A and B are shown with breaks. HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; IU/mL, international units per milliliter; S/CO, signal-to-cutoff ratio; ns, not significant.

Table 2. Serological response rates at months 12 and 24 by fibrosis stage

Outcome	Time point	Group 1 n/N (%)	Group 2 n/N (%)	Group 3 n/N (%)	Total n/N (%)	P
HBeAg clearance	Month 12	4/73 (5.48)	10/68 (14.71)	8/27 (29.63)	22/168 (13.10)	0.006
	Month 24	12/75 (16.00)	21/70 (30.00)	11/27 (40.74)	44/172 (25.58)	0.022
HBeAg seroconversion	Month 12	8/73 (10.96)	7/68 (10.29)	7/27 (25.93)	22/168 (13.10)	0.097
	Month 24	11/75 (14.67)	8/70 (11.43)	5/27 (18.52)	24/172 (13.95)	0.647
HBsAg decline > 1.0 log ₁₀	Month 12	9/74 (12.16)	17/67 (25.37)	6/27 (22.22)	32/168 (19.05)	0.123
	Month 24	12/75 (16.00)	26/70 (37.14)	7/27 (25.93)	45/172 (26.16)	0.015
HBsAg clearance	Month 12	1/74 (1.35)	3/67 (4.48)	1/27 (3.70)	5/168 (2.98)	0.536
	Month 24	4/75 (5.33)	7/70 (10.00)	2/27 (7.41)	13/172 (7.56)	0.568
Virological response (HBV DNA < 20 IU/mL)	Month 12	14/28 (50.00)	21/37 (56.76)	11/19 (57.89)	46/84 (54.76)	0.822
	Month 24	21/30 (70.00)	35/41 (85.37)	17/21 (80.95)	73/92 (79.35)	0.281

* $P < 0.05$; ** $P < 0.01$. HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B virus deoxyribonucleic acid; IU/mL, international units per milliliter.

Table 3. Fibrosis outcomes at 24 months of antiviral therapy by baseline fibrosis group

Change in fibrosis stage	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Total n (%)	χ^2	P
Progression	9 (19.15)	4 (8.51)	0 (0.00)	13 (11.40)	65.99	0.001**
Stable	38 (80.85)	13 (27.66)	1 (5.00)	52 (45.61)	65.99	0.001**
Improvement	0 (0.00)	30 (63.83)	19 (95.00)	49 (42.98)	65.99	0.001**
Total patients assessed	47	47	20	114	65.99	0.001**

** $P < 0.01$. Change in non-invasive fibrosis stage from baseline to month 24 was categorized as Progression (increase in fibrosis stage), Stable (no change), or Improvement (decrease in fibrosis stage).

0.995–0.999, $P = 0.017$), demonstrating that the rate of early HBeAg decline during treatment is significantly associated with long-term HBeAg clearance. The other included variables, namely baseline HBsAg < 1,500 IU/mL, baseline ALT, and APRI at month 3, were not independently predictive in the multivariate analysis ($P > 0.05$).

In summary, baseline liver fibrosis severity (particularly early cirrhosis) and HBeAg level at month 6 of treatment are independent predictive factors for HBeAg clearance at 24 months during Peg-IFN combined with NAs therapy.

Cumulative incidence of HBeAg clearance in patients with different fibrosis groups

Based on the results of the multivariate logistic regression

analysis, to further validate the predictive role of baseline liver fibrosis severity on HBeAg clearance, we compared the cumulative incidence of HBeAg clearance during the 24-month treatment period among different fibrosis groups. As shown in Figure 4 and Supplementary Table 5, the HBeAg clearance rate exhibited an increasing trend with worsening fibrosis severity: Group 1 (no significant fibrosis) was 16.00% (12/75), Group 2 (significant fibrosis) was 30.00% (21/70), and Group 3 (advanced fibrosis/cirrhosis) was 40.74% (11/27). Group 2 and Group 3 both showed significantly higher clearance rates compared with Group 1 ($P = 0.049$ and $P = 0.009$, respectively). The median clearance time for all three groups was 24 months. These results further confirm that baseline liver fibrosis severity is an important predictive factor for HBeAg clearance under Peg-IFN combined with NAs therapy, with

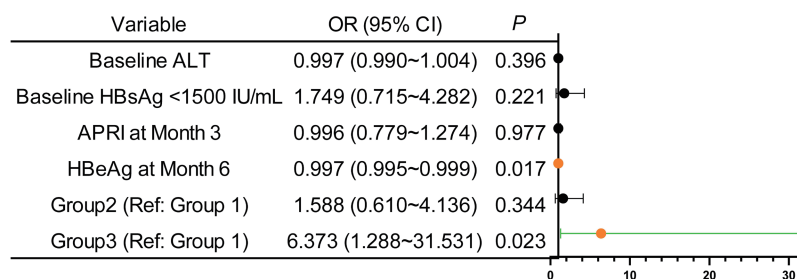


Fig. 3. Factors associated with HBeAg serological clearance in multivariate logistic regression analysis. The forest plot shows the odds ratios and 95% confidence intervals for factors associated with HBeAg clearance. Orange markers indicate statistically significant associations. $P < 0.05$ was considered statistically significant. HBeAg, hepatitis B e antigen; OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; IU/mL, international units per milliliter; APRI, aspartate aminotransferase-to-platelet ratio index; Ref., reference.

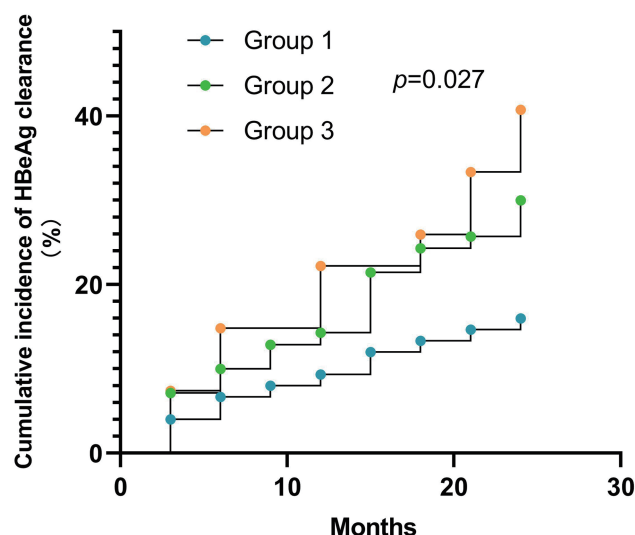


Fig. 4. Cumulative incidence of HBeAg clearance in patients with different fibrosis groups. Cumulative HBeAg clearance rates during 24 months of antiviral treatment were compared among the three fibrosis groups. Group 1, no significant fibrosis; Group 2, significant fibrosis; Group 3, advanced fibrosis/cirrhosis group. HBeAg, hepatitis B e antigen.

patients having more severe fibrosis demonstrating a higher cumulative probability of clearance.

Fibrosis outcomes at 24 months of treatment, stratified by baseline fibrosis group

According to the fibrosis outcome assessment at 24 months of treatment (definition detailed in the Methods section), the distribution of outcomes differed significantly among patients with different baseline non-invasive fibrosis stratification groups ($\chi^2 = 65.99$, $P < 0.01$), as shown in Figure 5 and Table 3. Most patients in Group 1 (no significant fibrosis) remained stable (80.85%), while 19.15% experienced fibrosis progression. In Group 2 (significant fibrosis), 63.83% achieved fibrosis improvement, and 27.66% remained stable. Notably, the regression proportion reached 95.00% in Group 3 (advanced fibrosis/cirrhosis). Overall, 42.98% of the entire cohort achieved regression, and 45.61% remained stable. These results suggest that the treatment regimen was associated with improvement in liver fibrosis indices, with patients having more severe baseline fibrosis showing a higher likelihood of improvement.

Dynamic monitoring of key non-invasive fibrosis indices (APRI and FIB-4) and liver function parameters further supported these findings. As shown in Supplementary Table 6, although significant differences existed in baseline APRI, FIB-4, ALT, AST, and PLT levels among the three groups (all $P < 0.01$), these parameters showed a trend toward improvement over the treatment course. By month 24, the differences between groups for all these indicators were no longer statistically significant (all $P > 0.05$). This dynamic change corroborates the fibrosis outcome results, collectively demonstrating the overall effectiveness of antiviral therapy in improving liver inflammation and fibrosis.

Sensitivity analysis results

To validate the robustness of the primary findings, a sensitivity analysis was conducted on 150 patients who completed at least 6 months of Peg-IFN α treatment. As provided in Supplementary Tables 7 and 8, the trend of the primary outcome

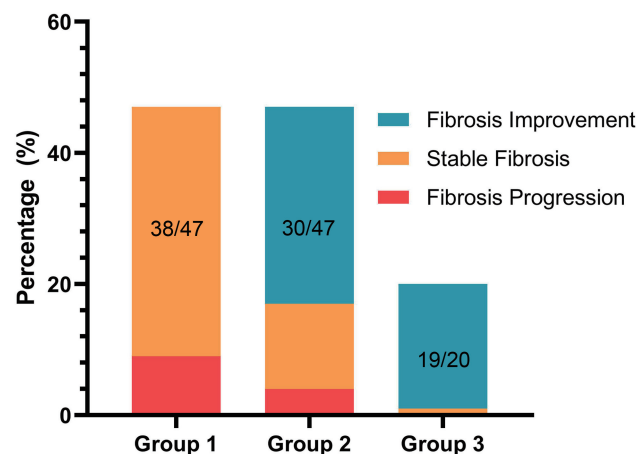


Fig. 5. Liver fibrosis outcomes at 24 months in patients stratified by baseline APRI/FIB-4 indices. Fibrosis outcomes were assessed based on changes in non-invasive fibrosis indices. Group 1, no significant fibrosis; Group 2, significant fibrosis; Group 3, advanced fibrosis/cirrhosis group. Numbers within the bars indicate the number of patients with fibrosis improvement/total number of patients assessed. APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 index.

(HBeAg clearance rate at 24 months of treatment) across different fibrosis groups in this subgroup remained consistent with the full analysis set ($n = 172$): Group 1, 18.84% (original result, 16.00%); Group 2, 28.81% (original result, 30.00%); Group 3, 45.45% (original result, 40.74%). The statistical significance of intergroup comparisons and the conclusion that “baseline fibrosis severity” served as an independent predictive factor in the multivariate analysis remained unchanged. These findings demonstrate that the study’s primary conclusions regarding the impact of baseline fibrosis severity on the effectiveness of the combination therapy regimen hold even after excluding patients with shorter treatment durations, further supporting the reliability of the conclusions. The treatment was generally well tolerated, with most adverse events being mild or moderate, including flu-like symptoms, transient hematologic abnormalities (decreased white blood cells, neutrophils, and PLTs), liver enzyme elevations (ALT/AST), and thyroid function changes. Importantly, no patients in the advanced fibrosis/cirrhosis progressed to decompensated cirrhosis during follow-up.

Discussion

To evaluate how baseline liver fibrosis severity affects treatment effectiveness, we conducted a retrospective study of HBeAg-positive CHB patients receiving Peg-IFN α plus NAs. The primary findings indicate that baseline liver fibrosis severity is associated with HBeAg clearance at 24 months of treatment, with higher HBeAg clearance rates and improvement in non-invasive fibrosis indices observed in patients with more advanced fibrosis. These results have important implications for optimizing clinical treatment strategies while emphasizing that APRI and FIB-4 improvements reflect non-invasive biochemical and structural changes rather than direct histological reversal.

Accumulating evidence in recent years has shown that Peg-IFN-based regimens—whether used as initial combination therapy with NAs for treatment-naïve patients¹⁷ or as an add-on/switch strategy for NA-experienced patients¹⁸—can markedly improve serological outcomes, notably rates of HBeAg and HBsAg clearance. This study further found

that patients with significant fibrosis or an advanced fibrosis/cirrhosis at baseline had significantly higher 24-month HBeAg clearance rates (30.00% and 40.74%, respectively) compared with those without significant fibrosis (16.00%), with clearance rates showing an increasing trend corresponding to fibrosis severity. Compared with monotherapy, Peg-IFN-based combination regimens demonstrate superior long-term benefits in HBeAg-positive CHB patients, including reduced risk of cirrhosis and enhanced serological responses.^{19,20} Previous studies have also confirmed that Peg-IFN treatment reduces liver necroinflammation in HBeAg-positive CHB patients, with fibrosis improvement observed particularly in responders.²¹

We speculate that the underlying mechanism may be complex. A potential concern is that the superior response in the advanced fibrosis/cirrhosis might be influenced by confounding factors, such as higher baseline ALT levels or a higher proportion of treatment-naïve patients, which are traditionally associated with better clinical outcomes. However, in our univariate analysis, neither baseline ALT nor treatment history demonstrated a statistically significant association with HBeAg clearance. Furthermore, baseline ALT was included as a covariate in multivariate analyses, allowing us to account for its potential confounding effect while confirming that fibrosis stage itself contributes to predicting treatment response.

These observations suggest that the favorable effectiveness in patients with advanced fibrosis may not be solely attributable to elevated baseline inflammation or treatment status. Instead, it is possible that fibrosis stage itself—potentially reflecting a distinct intrahepatic immune microenvironment—plays a role in predicting treatment response. More significant fibrosis is often accompanied by specific immune responses.²² Peg-IFN α , as an immunomodulator, may more effectively stimulate and synergize with pre-existing antiviral immunity in such an already immunologically active microenvironment, thereby promoting HBeAg clearance more efficiently. Furthermore, alterations in the intrahepatic microenvironment during fibrogenesis, such as extracellular matrix remodeling and cytokine network changes, may influence immune cell recruitment and function and the cellular environment for viral replication and antigen expression, allowing the combination therapy to exert unique immunomodulatory and antiviral effects in more fibrotic livers.²²

Notably, although significant differences in HBeAg clearance rates were observed among fibrosis groups, no statistically significant differences were found in HBsAg clearance rates or complete HBV DNA suppression rates. Similarly, HBeAg seroconversion rates remained low across all groups and did not differ significantly, although the trends mirrored those of HBeAg clearance. This suggests that baseline fibrosis severity may primarily influence the immune clearance phase against HBV (manifested as HBeAg clearance), while having a relatively limited impact on direct antiviral suppression dominated by NAs. HBsAg clearance, as a marker of more complete immune control, may require longer observation periods or be governed by other host or viral factors. Interestingly, patients in the significant fibrosis group exhibited a more pronounced HBsAg decline and a higher proportion of early rapid decline ($>1.0 \log_{10}$) during treatment, which may reflect additional suppression of surface antigen production due to the immunologically activated state in this group. However, this did not ultimately translate into higher HBsAg clearance rates, and the specific mechanisms warrant further investigation.

Another key finding is that the combination therapy effectively promoted improvement in non-invasive fibrosis indices, with the benefit positively correlating with baseline fibro-

sis severity. The proportion of fibrosis improvement reached 95.00% in the advanced fibrosis/cirrhosis and 63.83% in the significant fibrosis group. Interpretation requires caution, as APRI and FIB-4 incorporate aminotransferase levels (AST/ALT); the rapid decline—especially in the advanced fibrosis/cirrhosis—likely reflects both resolution of hepatic necroinflammation and potential structural regression. Patients with higher baseline inflammation may experience faster normalization of transaminases, driving a rapid mathematical reduction in these indices. While histological confirmation remains the gold standard, APRI and FIB-4 are recommended by World Health Organization and European Association for the Study of the Liver for longitudinal monitoring in resource-limited settings.^{23,24} Therefore, we used these indices to evaluate overall liver health improvement (biochemical plus structural), not to claim histological reversal.

Despite the composite nature of these indices, the observed improvements have significant clinical value. For patients with HBV-related compensated cirrhosis, finite Peg-IFN α therapy remains feasible and safe.²⁵ No patients in the advanced fibrosis/cirrhosis developed decompensated events during follow-up, supporting the safety of therapy. The “regression” observed here—viewed as a holistic improvement in liver health encompassing both anti-inflammatory and antifibrotic components—is closely associated with reduced long-term clinical risks, such as hepatic decompensation and HCC.²⁶ Dynamic monitoring data further corroborated this, showing that although baseline liver function and fibrosis indices differed among the three groups, ALT, AST, APRI, and FIB-4 levels in all groups tended to improve by month 24, with intergroup differences disappearing. This confirms that for patients with advanced fibrosis, the therapy confers dual benefits: alleviating necroinflammation and promoting structural remodeling, thereby modifying the disease trajectory.

The findings of this study have direct relevance for clinical practice. Peg-IFN α combination therapy can be considered for eligible HBeAg-positive CHB patients, even in the presence of significant fibrosis or advanced fibrosis/cirrhosis. On the contrary, these patients may represent a potentially advantaged population that can derive dual benefits from higher HBeAg clearance rates and improvements in non-invasive fibrosis indices. Previous studies also indicate that Peg-IFN is effective and safe in HBeAg-positive patients with advanced fibrosis; although some patients may not achieve sustained response, individuals with compensated advanced fibrosis or cirrhosis should not be excluded from Peg-IFN treatment.²⁷ This provides new evidence for developing individualized treatment strategies based on baseline fibrosis severity.

This study has certain limitations. Primarily, as a single-center retrospective investigation, it may be susceptible to selection bias. Secondly, liver fibrosis staging relied on non-invasive indices such as APRI and FIB-4, which, although widely used clinically, are less accurate than liver histology. Furthermore, details such as specific interferon dose adjustments and reasons for discontinuation during treatment were not fully incorporated into the analysis. Despite these limitations, this retrospective analysis provides novel evidence that baseline liver fibrosis severity may predict a more favorable response to Peg-IFN α plus NAs combination therapy in a specific patient population. Future studies are required to confirm these findings and explore the underlying biological mechanisms.

Conclusions

This study demonstrates that baseline liver fibrosis severity is a key independent factor in predicting treatment response

to Peg-IFNα plus NAs in patients with HBeAg-positive CHB. Patients with more advanced fibrosis achieved higher rates of HBeAg clearance and substantial improvements in non-invasive fibrosis indices. The robustness of these primary conclusions was supported by sensitivity analyses. These results suggest that baseline fibrosis assessment has clinical value in optimizing patient selection for Peg-IFN-based combination therapy. Future prospective, multicenter studies with long-term follow-up and incorporation of histological or multi-omics approaches are warranted to validate these findings and elucidate the underlying mechanisms.

Supporting information

Supplementary material for this article is available at <https://doi.org/10.14218/JCTH.2026.00093>.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception of the article, organization of the literature, writing of the manuscript (YZ, FC, SJW), figures and tables (XW, SYW, LY, ZG, WD), review and revision of the manuscript, and financial support (ML). All authors read and approved the final version of the manuscript.

Ethical statement

This retrospective analysis utilized data from an established prospective cohort. The original study protocol, including informed consent procedures, was reviewed and approved by the Ethics Committee of Beijing Ditan Hospital (Approval No.: Jing Di Lun Ke Zi 2018 No. 023-01). The original study was conducted in accordance with the Declaration of Helsinki (as revised in 2024). The use of these data for the present analysis was covered by the original ethical approval and informed consent.

Data sharing statement

Data are available from the corresponding author upon reasonable request.

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